SCIENCE FOR EVERYONE

V. M. DILMAN

THE GRAND BIOLOGICAL CLOCK

MIR

В.М. Дильман

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V.M. Dilman

The Grand Biological Clock

Translated from the Russian
by M. Rosenberg

Translation edited by T. Juswigg

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Introduction

From individual discoveries to the once lost and continuously slipping away concept of the integrity of Nature.

There are several "eternal questions" that Homo sapiens seeks to answer. Apparently, the most vital question concerns the causes limiting the lifespan of every individual, or, in other words, the question of the causes of natural death. The causes of death in animals living in their natural environment are their enemies, diseases, and hunger, i.e., practically none of them reach the age when natural death occurs. However, since the origin of civilization, humans have more often been able to observe a phenomenon defined by the word "aging". Historians note that since that time the wish to extend the human lifespan arose, i.e., aging was gradually considered to be the cause of natural death. Currently, the division of the causes of death into two categories, i.e., death from external causes, including diseases, traumas, hunger, etc., and death from internal causes, primarily aging, still holds, although these concepts are usually described in another

way. First of all, today, two values that characterize the lifespan are strictly discriminated: the anticipated duration of life, or, to be less strict, the value of the average lifespan; and the value of the maximal lifespan that is characteristic of one or the other species, i.e., the species lifespan.

In the twentieth century the average lifespan increased greatly in industrially developed countries, especially in the second half of the century when mortality, attributed to various infectious diseases, decreased sharply. As a result, an increasing number of people today reach the age of 65 years and more. Thus, a new phenomenon is gradually arising: a community with a steadily increasing number of elderly people. It would seem that the eternal dream of prolonging life is gradually being realized. Nevertheless, the social and psychological results of this dream are not that advantageous. As a matter of fact, the number of people suffering from chronic diseases, primarily cardiovascular diseases, malignant tumours, and diabetes mellitus, increases in parallel with the extension of the average lifespan. These three categories of diseases are the causes of death in 80 people out of every 100 adults who have reached middle age; therefore, they are currently called the major noninfectious human diseases. Thus, the decrease in mor-

tality in middle-aged and elderly people has led to an increase in the incidence of diseases. And what is more, the incidence of dangerous chronic diseases has increased, becoming a heavy burden for each individual and for society as a whole. Society has had to allot more and more material resources for health care and social security; however, in spite of the tremendous material investments, the situation has not improved. For example, in the USA the total mortality from cancer increased by 54.7% in the period from 1962 to 1982; the mortality per 100 000 people increased by 25%; and the mortality calculated by taking into account the changing age of the population, by 8.5% (J.C. Bailar, E.M. Smith. *Progress Against Cancer? New Engl. J. Med.*, 1986, 314, p. 1226).

Everyone is beginning to understand that additional efforts are required to change the situation. But, first of all, we must learn why the major diseases emerge and why they are progressively spreading. Modern medicine gives the following answer. All the known diseases, despite their variety and plurality, are engendered by only two categories of phenomena: a) external damaging agents, including bacteria, viruses, traumas, stress, toxic substances, (such as chemical carcinogens, i.e., chemicals producing cancer), radiation, hunger, overnutrition, lack of vitamins, etc.;

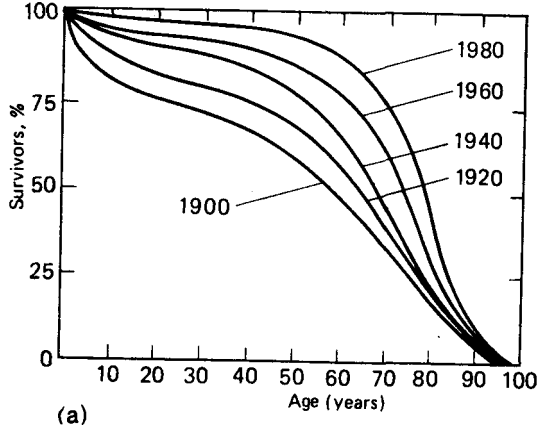
and b) genetic inborn defects, which, in their turn, appear most often because of the action of external damaging agents such as toxic substances, carcinogens, and radiation, on the organism. Thus, modern medicine maintains that there are only two reasons or two models for the origin of diseases: ecological and genetic.

From this point of view all diseases are random, i.e., they may or may not affect the individual because the action of external damaging agents is a random phenomenon, although the probability of this random event increases with aging of the organism, primarily, as a result of increased exposure to pathogenic agents.

Proceeding from this theory, it is believed that it is possible to spare people these diseases, including the major noninfectious diseases of modern times. To this end, the external causes of each disease and the "risk factors" that increase the probability of the disease occurring must be determined. Then either the external harmful agents must be eliminated, or their pathogenic effect on the organism must be prevented.

In the 19th and 20th centuries these ideas invariably led to the elimination of various infectious diseases as the leading causes of death, and then to the elimination of many noninfectious diseases, e.g., diseases caused by a lack of vitamins.

Therefore, it currently seems that the measures based on the ecological and genetic models will be able to prevent all diseases. Accordingly, the average lifespan will increase in parallel with the elimination of the major causes of death of the modern human. For example, it is estimated that if cardiovascular diseases are prevented in the USA, an increment of about 12 years will be added to the lifespan; and, if cancer is eliminated, about two more years will be added. Finally, if all the causes of death due to diseases and accidents are eliminated, people will be able to live to about 100 years of age. Life will end in natural death, i.e., death not due to diseases but due to aging, which gradually deteriorates all the physiological indices of the organism. The rate of this deterioration is frequently described by estimations that were published in 1825 by Gompertz, a British statistician who worked in an insurance company. Gompertz calculated that human mortality doubled every eight years beginning with the age of 30. As a result, the probability of dying from any disease increases exponentially with age. This increased vulnerability to diseases is explained by the aging of the organism, which annually loses, as it is currently believed, from 0.8 to 0.9% of the functional capacity that existed at the age of 30 (Strehler and Mildvan, 1960).



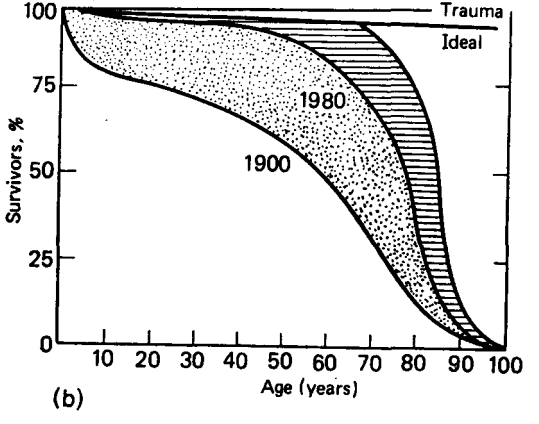


Fig. 1. *a*—Survival curves in the USA in the 20th century (J. Fries, 1983); *b*—survival curves in the USA in the 20th century and prognostication of an "ideal" survival curve (J. Fries, 1983).

The role of diseases as the basic factor for determining the average lifespan, and the role of aging as a factor limiting the species lifespan are frequently illustrated by comparing two graphs (Fig. 1*a*, *b*). Fig. 1*a* demonstrates the changes in the survival curves in the twentieth century in an industrially developed country. These survival curves gradually approach right-angled curves. This corresponds to a decrease in mortality in young and middle-aged adults, which results in an increase in the average lifespan in the twentieth century. Fig. 1*b* illustrates a situation that assumes the elimination of diseases as the major causes of death. Under these conditions, the lifespan of an individual should approach the species lifespan, which, according to the modern doctrine, is determined not by diseases but by normal physiological aging. In other words, the modern theory of medicine predicts that, in principle, it is possible to eliminate diseases by following the traditional methods and, as a result, to make the average lifespan approach that of the species lifespan.

As far as the possibility of expanding the limits of the species lifespan is concerned, it is believed that progress in this direction will depend on whether or not it will be possible to control the aging process. From the author's point of view

this delimitation of diseases and aging is the main mistake in the traditional theory of medicine and, consequently, is the reason that makes it impossible to free the process of aging from associated, or, more precisely, characteristic, diseases. And what is more, the suggested traditional measures will never yield positive results if the mechanisms of formation of the major noninfectious human diseases, and, correspondingly, the mechanisms determining the length of the species lifespan, which the author has described, are not taken into consideration.

Indeed, why do we age and is natural death that is caused by debility without complications due to diseases possible? What determines the limits of the species lifespan, and is it possible to increase the latter? Finally, is it possible to retard aging? For people of all times have always dreamed of prolonging not life itself but the period of youth, which is associated with the blossoming of all the potentialities of the personality. According to various sources, as far back as the fourth millenium B.C. there was a mythological hero of shummers who hoped to find plants that could grant eternal youth.

The answers to all these questions are the main theme of this book. It should be stressed that the answers given here differ substantially from the hypotheses and theories on the causes of aging and nat-

ural death that are found in the modern literature. Despite the variety of these theories, they can be divided into two categories: a) those that explain that aging is genetically programmed; and b) those that state that aging arises as a result of the accumulation of stochastic events in the body that are conditioned by impairment of the cells, tissues, and systems of the organism.

Certainly, protective systems that suppress the formation of free radicals and repair the damage have evolved. A certain acceptable balance between the extent of the damage and the mechanisms for their prevention and repair has been established in each animal species. Accordingly, the more actively one or the other protection system functions, the greater the maximal lifespan; this is clearly traced in such close species as primates, including the human (Cutler, 1980). However, the biological systems of protection do not function reliably enough to prevent all the damage; therefore, it continuously accumulates in the organism. Consequently, in this sense aging begins simultaneously with the conception of the individual. And what is more, there is the permanent threat that an impairment of the genetic apparatus of the cell may cause its malignant transformation (Chapter 10), or form an atherosclerosis obliterans (Chapter 9). Thus, along-

side the ecological and genetic models of the origin of diseases, it is necessary to recognize the existence of the accumulational model, according to which it is not the external, but the internal, damaging agents that are the cause of impairment (Chapters 6 and 12). In addition, the stochastic accumulational mechanisms of aging apparently participate in the formation of other regular mechanisms of diseases and aging that the author has described. But, before discussing the nature of these mechanisms, it is necessary to mention the second traditional approach, wherein aging is considered to be a genetically programmed phenomenon. Indeed, if aging is genetically determined, then from this point of view it would be most simple to explain why each species, including the human, has its own potentially maximal lifespan, i.e., a strictly fixed limit. Thus, this limit is greater in humans than in higher primates, while in primates it is greater than in rats, and so on. Hayflick (1961, 1985) believes that these differences are determined by changes that occur in the genetic apparatus of each cell as a result of which there is a limit that restricts the number of potential cell divisions. And, the greater the number of potential doublings of cell populations, the longer the species lifespan. Hayflick's limit is about 50 cell doublings for a human; about 10 for

a rat; and about 80 for a tortoise. Though Hayflick's limit is never exhausted within a species lifespan, the decrease in various functional capacities of the cell correlates with this limit, and, as it is believed, determines the picture of aging. However, objections on the basis of common evolutionary principles can be made in regard to all the variants of the genetically determined theories of aging.

In the light of evolutionary processes, wherein natural selection is the key factor, there cannot be any program or gene that specifically provides for the onset of aging or death. On the contrary, natural selection has always been directed towards extending the lifespan, i.e., the longer the given specimen lives, the greater the probability of leaving more progeny, and, consequently, the greater the probability that precisely its genes, including the genes that determine the capacity for a longer lifespan, will accumulate in the population. Hence, natural selection does not favour aging. But aging exists in reality. When considering this contradiction, it is necessary to explain, first of all, why the phenomenon of aging has not been eliminated in the process of natural selection. According to the most elaborated evolutionary hypothesis, aging is an inevitable, though an indirect, consequence of natural selection. In particular, Peter Medawar has shown

that in the case of the accidental death of animals on a large scale (which is observed in real conditions), potential immortality gives such a population no advantages as compared to a population with a finite lifespan. Therefore, the pressure of natural selection is directed towards optimization (improvement) of only the periods of development and reproduction of the organism as applied to the habitat of one or the other species.

It is also assumed (Williams, 1957) that given the realization of these requirements, the onset of aging can be associated with genes whose effect is favourable at early stages of development (ontogenesis) and in the reproductive period despite the fact that their functioning causes disturbances at a later age. The presence of a selection process that delays the manifestation of the harmful properties of the genes if these genes cannot be eliminated is assumed by another evolutionary hypothesis of aging (Medawar, 1952). In other words, selection will always contribute to greater viability in youth even at the cost of an adverse effect during the subsequent periods of life. The phenomenon of aging is the result of this delayed (or pleiotropic, i.e., producing many) effect.

The concept of delayed manifestation of the impairing action of genes as a result of aging is considered to be very success-

ful, because it describes the direction of influence of natural selection and, at the same time, explains the onset of aging and natural death without tying them to the concept of their being genetically programmed. However, the difficulties in accepting this hypothesis are associated with the fact that what "switches over" the action of the genes from a useful to an impairing effect and when this occurs are still unknown. Therefore, currently it is believed that the genetic program is not realized "from the beginning to the end" but has a "beginning without an end", i.e., the cellular functions decrease or stop more or less randomly like an accidental breakdown of a new car which is poorly repaired or looked after (Hayflick, 1985). Correspondingly, a combined hypothesis is suggested that describes the destruction of the genetic program as a result of the accumulation of damage. In addition, it is possible that the existence of the Hayflick's limit is conditioned by the accumulation of cholesterol in the plasma membrane of the cells (Chapter 17), i.e., it has no relation to the cellular program of aging.

At the same time, this author's theory makes the concept of the pleiotropic (dual) properties of genes in explaining the origin of aging unnecessary because, according to this theory, both effects (useful and harmful) are the result of quantitative changes

in the same mechanism that at first supported realization of the developmental program, and then transformation of this program into a mechanism of aging and disease formation. Thus, the pleiotropic effect is realized without pleiotropic genes. The new theory also explains why the species lifespan cannot be a strictly fixed limit and, on the contrary, should change with the generations (i.e., in phylogenesis) depending on the extent of the external causes of death. This means that the limits of the species lifespan can be increased by directed medicinal measures.

This theory makes it possible to state that there is no genetic program of aging that leads to inevitable, i.e., natural death, although this phenomenon arises with a regularity characteristic of a genetic program. Finally, the new theory demonstrates that normal aging should always combine with the onset of the major diseases. Hence, the expectation that natural old age can occur without diseases, i.e., the expectation on whose basis, as we have noted above, the future development of medicine is prognosticated, is incorrect. On the contrary, it is possible to eliminate the major diseases only by taking control of the mechanisms that lead to aging and age-related diseases. To clarify at least in the most general form what this new theory is based on, it is necessary to

recall one of the fundamental laws of biomedicine, formulated by Claude Bernard (1869): the constancy of the internal environment, or homeostasis, (by W. Cannon, 1929) is an obligatory condition for maintaining the life of an organism.

Indeed, an organism can only preserve its vital activity given relatively stable parameters of the internal environment, e.g., given a certain body temperature, arterial pressure, blood glucose concentration, etc. If the value of the given parameters exceeds a certain limit, then this state is determined as a disease: examples corresponding to the parameters mentioned above are fever, hypertension and diabetes mellitus, respectively. At the same time, any one of these diseases can be the cause of death. Therefore, in this author's opinion, any stable disturbance of the homeostasis is a disease, because a disease is any process in the organism that increases the probability of death.

At the same time, a living system in equilibrium cannot ensure the additional inflow of energy and materials necessary for the growth and development of the organism. In other words, stability prohibits development. Therefore, alongside systems that maintain homeostasis at each given moment of time, there are systems in developing organisms that ensure deviation of homeostasis in time. Corre-

spondingly, there is a law that this author has termed the law of deviation of homeostasis.

The law of deviation of homeostasis was formulated in 1979 and it led to the creation of the ontogenetic model of aging and major diseases formation (see below). However, the concept itself, which later became the basis for the neuro-endocrine (hypothalamic) mechanisms of aging, was first published by the author in the Soviet literature in 1958, and in the foreign literature in 1971 (*Lancet*). Great contributions to investigations on the neuro-endocrine mechanisms of aging were made by C. Finch (1973, 1976: neurotransmitter mechanism), G. Roth (1974, 1978: receptor mechanism), J. Meites (1976: changes in the reproductive system), G. Riegle (1972, 1973: changes in the adaptational system), P. Asenheim (1964: heterochromous transplantation of the ovaries), A. Everitt (1973), and other researchers. The ideas of R. Cutler (1976, 1978, 1984) warrant special attention and are discussed in Chapter 11 of this book.*

The physiological mechanisms that rea-

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* The basic bibliography is given in the following monographs written by this author: *The Law of Deviation of Homeostasis and Diseases of Aging*, John Wright PSG Inc., Boston, 1981; and *Four Models of Medicine*, Meditsina, Leningrad, 1987.

lize the law of deviation of homeostasis meet the requirements for the growth and development of the organism. However, after the completion of development, the mechanisms that realize these processes continue to function. Therefore, the internal factors that provided a disturbance in the homeostasis in order to ensure the organism's development continue to function after development has ceased inducing a more and more stable disturbance in the homeostasis. This gradually leads to certain diseases that are incompatible with the continuation of life.* These diseases are: the climacteric, hyperadaptosis, obesity, prediabetes, atherosclerosis and its complications, metabolic immunodepression, auto-immune diseases, hypertension, mental depression, premyxedema, cancrophilia. They represent the sum of metabolic conditions that contribute to the devel-

* There is a superficial similarity between this author's theory and that of Bidder (1932) according to which aging is a result of continuing action of the regulator that controls growth despite a stop in the increase of the linear sizes of the body. But in this author's concept the cessation of growth is not a key element because deviation of homeostasis in the reproductive, energy, and adaptational systems occurs beginning with the early stages of ontogenesis, including development of the fetus, or, for example, the mechanism of death of the Pacific salmon after spawning (Chapter 3).

opment of cancer, and, finally, normal aging itself. Indeed, there is a regular disturbance in the homeostasis during aging, mainly in the energy, reproductive, and adaptational systems (see Chapters 5 through 8). Accordingly, aging is a disease, or, to be more precise, the sum of diseases of the homeostasis conditioned by ontogenetic mechanisms and the accumulation of damage in the organism (Chapter 11). From this point of view, the exponential increase in the probability of death with age (see above) is not only a consequence of diseases, but also the advance of aging as a disease.

Those readers who are familiar with medicine will note the unusual nature of the list of major diseases: this author included the climacteric and aging, which in traditional medicine are not considered to be diseases, as well as some new diseases, such as hyperadaptosis, metabolic immunodepression, cancrophilia, prediabetes, premyxedema, and mental depression were also included in the category of major diseases.

The changes introduced are based on the following circumstances. In traditional medicine the major noninfectious diseases are classified as such because they are the major causes of death in modern humans. The basic diseases in this author's list however are those that, irrespective of

ecological and genetic factors, always arise in humans at the same rate, being a by-product of the developmental mechanism. Therefore, alongside the ecological, genetic, and accumulational models of the development of diseases, there is also an ontogenetic model (from the word "ontogenesis", which means the development of the individual organism). Diseases that arise according to the ontogenetic model form the group of regulatory diseases, unlike the diseases that occur as a random event in all the other cases of their development. Therefore, taking into consideration the ontogenetic mechanism of the diseases listed above, this author has called them "normal diseases". This book explains how "normal diseases" begin to develop after the age of 20-25, i.e., immediately after the maturation of the organism has ceased.

In light of this thesis it is easy to understand the danger of the traditional concept, according to which each age period of the adult is characterized by a norm of physiological parameters. This thesis makes it possible not to counteract the ontogenetic mechanisms of aging and age-related diseases. In reality, the norm is the level of physiological parameters at which mortality is minimal from diseases conditioned by disturbed parameters. In other words, it is not enough to feel healthy, it is necessary to be normal (Chapter 13).

However, the mechanisms supporting the metabolic growth requirements of the fetus during pregnancy, the mechanisms of accelerated development of the organism, and the mechanisms of growth and sexual maturation are also based on progressive deviation of homeostasis. Therefore, ontogenesis not only defines the biological development of the organism; it is also a clinical problem. In particular, the external noninfectious pathogenic factors, such as stress, overeating, excess illumination, and insufficient physical activity, cause diseases that make up the cluster of major diseases, because they accelerate the ontogenetic mechanisms of their development. In this respect it should be noted that the major diseases with the same clinical symptoms develop by four different mechanisms. For example, atherosclerosis results from overeating (ecological model), a deficit of receptors ensuring cholesterol transport into the cells (genetic model), impairment of the internal wall of the arteries (accumulational model), and the regular age-related shift in metabolism, in particular, the age-related increase in the cholesterol content in the blood (ontogenetic model).

The major part of this book covers the concepts and data that the ontogenetic theory of aging and age-related diseases as well as natural death are based on. In

addition, the new theory is in good agreement with the theories that explain the phenomenon of aging and natural death by the accumulation of damage in the organism (Chapter 11).

It is necessary, however, to find an explanation for the fact that effective systems of protection have not evolved that would support the existence of the organism indefinitely by eliminating the damage that accumulates. According to the disposable somatic theory of aging, the evolution of such protection systems is impossible because of the necessity of distributing energy between the processes of growth, maintenance of vital activity, reproduction, and protection (Kirkwood, 1985). At the same time, taking into consideration that the ontogenetic mechanisms lead to cessation of life long before the accumulation of damage becomes incompatible with the existence of the organism, perfect protective mechanisms could not develop because they would not have provided the species with the advantages of selection. At the same time, the ontogenetic mechanism of diseases and natural death, as a by-product of the developmental mechanism, in essence improved in parallel with improvement of the developmental mechanism during the evolution of each species. In other words, onto-

genetic diseases represent a peculiar peak of evolution.

The aforementioned allows one to perceive the new perspectives disclosed by the theory of four models explaining the origin of the major diseases. In particular, this theory demonstrates that the average lifespan is determined by ecological and genetic factors, while the maximal lifespan is conditioned by ontogenetic and accumulational mechanisms. Thus, the maximal lifespan is not fixed: it can change depending on the rate of the ontogenetic and accumulational mechanisms. For example, increased death from external causes should lead in the succession of generations to a decrease in the maximal lifespan. And, on the contrary, retardation of these mechanisms should expand the limits of potential life. In other words, it is not in dreams but in reality that one can live much longer than is predetermined by the current stage of human evolution.

Control of the ecological and genetic causes of the major diseases is not sufficient, however, to reach this goal. We must learn to influence these diseases as an integral interwoven group of diseases as a whole. This can only be achieved by influencing the common, integral mechanism of development of the major diseases, i.e., the rate of aging. This conclusion has determined the title of the book—*The*

Grand Biological Clock —whose rate predetermines the species lifespan and, correspondingly, the natural causes of death of each individual. The Russian edition of the book is subtitled *An Introduction to Integral Medicine* because the historical and artificial division of medicine into individual specialities must be overcome by the integral interpretation of physiological and pathological processes. The delimitation of the mechanisms of the major diseases must also be dispensed with: their common character, as is shown in this book, determines practically identical causes of natural death in such diverse species as salmon, rat, and human.

The absence of clear boundaries between the norm and the disease, between pregnancy, accelerated development and the major diseases, between the stochastic processes of aging and regulatory (determinative) mechanisms of development, between the internal and external causes of the major diseases, and between the law of constancy of homeostasis and the law of deviation of homeostasis, all of which are realized by the same mechanisms, still make up an incomplete list of dialectic contradictions that are elucidated by the author in this book. The general measures of prophylaxis and treatment for the major diseases are also presented. In particular, on the basis of the new theory, the age-

related decrease in immunity could be improved or even recovered in 60-70% of the population suffering from it. The same individuals experience a decrease in the risk factors of atherosclerosis, and other benefits (*Four Models of Medicine*, Meditsina, Leningrad, 1987). But the possibility of experimentally decreasing the incidence of benign and malignant tumours by 2.5 to 4 times, and of, at the same time, extending the lifespan of the animals by 20 to 25% is even more impressive (see Chapter 16). As stated above, based on the example of what has occurred in the USA, it is clear that currently when prophylaxis is based only on ecological principles, an increase in the average lifespan coincides with an increase in the incidence of cancer.

Hence, the urge to understand nature as an integral system forms the basis of the concept discussed in this book. This urge has been inherent to science from the very beginning. It is expressed most vividly in the concepts of the philosophers of Ancient Greece, who distinguished between the laws of dialectics and the unity of the world. In addition, nothing has contributed more to studying nature than the specialization of sciences, and nothing has prevented understanding nature more than the division of the integral concept of nature based on the principles of specialization.

Chapter 1

Hierarchy of Control in the Organism: the Role of the Hypothalamus

> Hypothalamus—remember this complicated word. It is a miracle of nature, being a hybrid of the nervous and endocrine systems, the junction of two worlds, viz., the internal and the external.

Just as a house is built of bricks, a body is constructed of cells and tissues and systems that connect them. Together they make up the integral supersystem of an organism.

Myriads of cellular elements would not function as a single whole if there were not a refined mechanism of regulation. A specific role in this regulation is played by the nervous system and the endocrine glands. But the intricate regulatory mechanism consists of several stages and the first takes place on the cellular level. The cell is the base of life: this old saying holds a still deeper meaning today.

Each cell is a miniature sustainer of life which has subordinated its own freedom to the activity of the organism as a whole. It contains genetic information sufficient to reproduce the entire organism. This information is recorded in the structure of deoxyribonucleic acid (DNA) and is contained in the chromosomes in the nu-

cleus. For this reason only the nucleus was considered for a long time to be the regulator of vital activity in the cell. Later, the significance of other cellular components was understood, and scientists were faced with an astonishing picture.

Formations—mitochondria—were discovered in the cells of all higher organisms, which functioned like a furnace that burns the fuel used by the body: carbohydrates (glucose) and fats (fatty acids). The mitochondria have their own apparatus of heredity and division. A large amount of data suggest that at some stage of evolution mitochondria existed independently; later they combined with the primitive cell, providing it with a perfect method for burning fuel, thereby increasing its energy resources.

A cell has intracellular regulators, whose structure is the same in microbes and in the cells of higher organisms. One group of these regulators is formed from the products of glucose metabolism (cyclic nucleotides), whose main representative is cyclic adenosine monophosphate (or cAMP); the second group is produced from the metabolic products of fatty acids (prostaglandins). Thus, the energy substrates form the basis of an intracellular regulatory system.

Nature has provided the cell with many devices and mechanisms but hardly anyone

expected that the cell membrane was so important. It seemed at first that the membrane simply forms an external boundary and protects the interior of the cell, passively ensuring the supply of necessary substances and the elimination of wastes. But if the cell membranes had only a bounding function, then, for instance, a signal to intensify the activity of the cells in the liver would be freely transmitted to all the body cells, since the energy system of all the cells is designed in the same way. This would result in chaos. In reality, the membrane of each cell is constructed in such a manner that it perceives only the signals addressed to it.

In general, a cell membrane consists of lipids, mainly cholesterol, which creates as if the framework of the membrane and phospholipids. The structure of this framework also contains proteins and molecules of sugar. All together they form structures that perceive the signals from the medium washing over the cell. These structures, which are called receptors, are sensitive to certain signals and insensitive to others. Cellular activity, division, etc. change in response to the signals transmitted from the membrane receptors. Thus, owing to the membrane, the cell responds only to the signal it needs, or, in other words, coordinates the first level of regulation, the intracellular level, with the

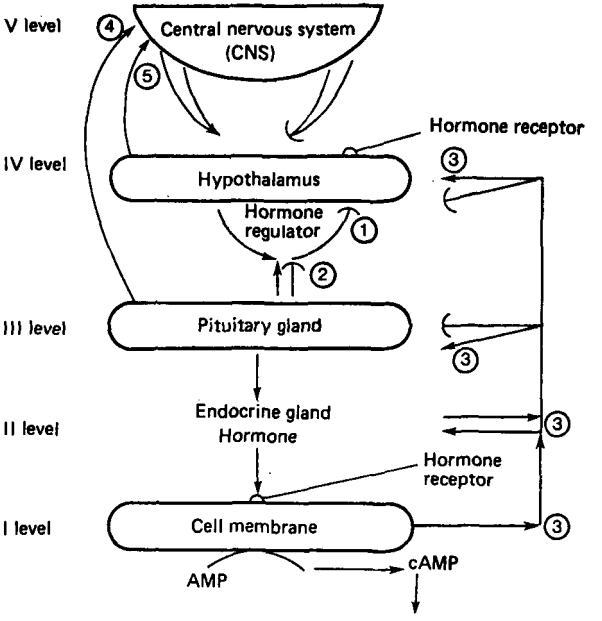

Fig. 2. Levels of neuro-endocrine regulation in an organism: I—intracellular level (scheme of cell membrane, hormone receptor (HR), and cyclic AMP (cAMP)—transmitter of action of hormonal signal); II—level of peripheral endocrine glands; III—hypophyseal level; IV—hypothalamic level; V—level of central nervous system; 1—ultrashort loop of feedback mechanism—effect of hypothalamic hormones on hypothalamus; 2—short loop of feedback mechanism—effect of hypophyseal hormones on hypothalamus; 3—long loop of feedback mechanism—effect of hormones of peripheral endocrine glands and products of metabolism (glucose, fatty acids, etc.) on the pituitary gland and hypothalamus; 4—regulation of activity of central nervous system by the pituitary gland; 5—regulation of activity of central nervous system by hypothalamus.

requirements set by the organism before the cell (Fig. 2).

The second level of regulation, the supracellular one, is effected by hormones. Hormones are special substances produced mainly by the endocrine glands; they are released directly into the bloodstream and regulate some aspects of metabolism of cells that are sensitive to them. Hormones function first of all to maintain a constant internal environment in the body.

We all know that life originated initially in an aqueous environment, and it is amazing to learn that the composition and concentration of salts (ions) washing over the cell are practically the same as in the saline medium of the world ocean in the Precambrian when the structure of the modern cell developed in the process of evolution. The composition of cells remained constant for millions of years despite their complex conversion into specialized tissues and organs during the subsequent evolution of living nature.

The sodium and potassium concentration in the blood, controlled chiefly by the adrenal glands, is strictly regulated throughout the entire life of the individual. Even age-related diseases are unable to cause essential changes in the concentration of these vitally important elements. It seems that the mechanism of death disregards certain indices of the internal en-

vironment, which are as important for the single cell in the primary world ocean as for the nerve cell in the human brain. These indices are protected so carefully probably for the sake of preserving life itself.

This circumstance explains to a considerable extent the great freedom in the activity of other endocrine glands, viz., those that participate in supporting the development of the organism. Furthermore, it is obvious that development requires the coordinated functioning of the endocrine glands. Therefore, in higher organisms, including Homo sapiens, a special endocrine gland unites the activity of several glands, thus resembling a control panel. The integration of the endocrine glands is accomplished by the pituitary gland, which is lodged in the sella turcica. The latter is well-protected by bones directly under the cerebral cortex, in the very centre of the cranial cavity.

Each peripheral endocrine gland is connected to the pituitary gland by a specific hormone-regulator. A number of individual systems are thus created, for example: the pituitary gland—sex glands, the pituitary gland—thyroid gland, and the pituitary gland—adrenal glands. Interaction between these systems is realized at the level of the pituitary gland. Hence, the pituitary gland effects the third level of regulation in higher organisms.

Although it regulates the endocrine glands, the pituitary gland is "blind" to the outside world. This regulator can receive signals informing it of what is happening in the body, but it has no direct connection with the external environment. In addition, to ensure that the external environment does not continuously disrupt the vital activity of the organism, it is necessary that the organism be able to adapt to the changing conditions.

We "learn" about the outside world through our skin, eyes, olfactory, auditory, and gustatory organs. The sense organs transmit the information to the central nervous system. But if, for example, the receptors of the skin cells record a drop in the ambient temperature, this is still not enough to prevent freezing. The decrease in the temperature must be conveyed to the organs that can increase the production and reduce the consumption of heat in the organism. The regulator that transmits information perceived from the outside world to the working organs, to the respective cells of various tissues, is the hypothalamus.

It is a complicated word—hypothalamus—but it should be remembered.

The hypothalamus is a miracle of nature.

On the one hand, it consists of typical nervous tissue made up of neurons, i.e., cells of the nervous system. These cells

are connected with all parts of the nervous system by means of numerous fibres. Therefore, everything that the nervous system "knows" about the external or internal world of the organism is easily and rapidly conveyed to the hypothalamus.

On the other hand, the hypothalamus is a typical endocrine gland that secretes special hormones. These hormones regulate the activity of the pituitary gland. Furthermore, the hypothalamus sends its hormones to distant parts of the body where they perform a regulatory function.

Thus, if the central nervous system receives a signal from the sense organs, the signal is transmitted to the hypothalamus, which, in turn, sends it to the pituitary gland, and from there it is finally forwarded to the working organs. Sometimes the hypothalamus exerts a direct effect on the body tissues via the nervous apparatus, or via the hypothalamic hormones. Thus, owing to the hypothalamus, interaction between the external and the internal world of the organism is realized.

The hypothalamus is the concrete site of the junction of two worlds. Nature created this unique structure for this special link between the external and internal environments, and it is a hybrid of the nervous and endocrine systems. Owing to its unusual design, the hypothalamus converts rapid signals from the nervous sys-

tem into slow, but specific reactions of the endocrine system.

On the face of it, the existence of both the pituitary gland and the hypothalamus may seem unnecessary. One would think that hypothalamic hormones could directly influence the organism without the intermediate link—the pituitary gland. But if this were the case, the hypothalamus would be considerably hampered as a regulatory organ. Quite a large number of hormones are necessary to influence the processes occurring in the body. As a result, the hypothalamus would exert much effort on the elaboration of hormones, and its potential for regulation would correspondingly decrease. The action of hypothalamic hormones, is, in fact, a continuation of the nervous impulse, and these hormones render precisely this regulatory effect on the pituitary gland. The absence of certain functions in the hypothalamus allows it, after transmitting a signal to the pituitary gland, to become free to perceive new signals from the external and the internal world.

Thus, the seemingly burdensome doubling of similar functions in the hypothalamus and pituitary gland creates in reality optimum conditions for regulation. Hence, the fourth level of regulation in the organism is accomplished at the level of the hypothalamus (Fig. 2).

The central nervous system, including the cerebral cortex, accomplishes the fifth level of regulation.

Incessant changes in the external environment demand continuous adaptation of the body functions. The same concerns regulation associated with consciousness or the performance of arbitrary activity. Therefore, it is natural that signals transmitted from various parts of the brain influence the activity of the hypothalamus. In addition, the activity of the hypothalamus as a part of the brain is also controlled to a certain extent by other parts of the nervous system. And finally, a special endocrine gland—the pineal body—which is also in the brain, renders a regulating effect on the hypothalamus, changing in particular its sensitivity to hormones.

Nevertheless, it is the hypothalamus and not other parts of the nervous system that is the central regulator of the internal environment of the organism. Signals from various parts of the brain first reach the hypothalamus where they seem to be filtered, and then the necessary information is transmitted to the body in the form of hypothalamic signals.

What can the significance of the hypothalamus be attributed to? First of all, the hypothalamus is the principal regulator of the vegetative or autonomic functions (occurring subconsciously).

Under normal conditions many functions are accomplished automatically, continuously, and with strict regularity. In this respect the influence of the central nervous system, which responds to environmental changes and to the still more changeable world of senses and thoughts, is unnecessary and inappropriate and would interfere with that which should be performed by its own internal laws. For example, if the cerebral cortex is removed from a rat, the reproductive function can still be realized, i.e., fertilization, normal labour, and feeding of the offspring. This indicates that the hypothalamus is the principal level of regulation for the reproductive function. On the other hand, if a rat is subjected to extreme emotional stress induced, for instance, by shrill sounds, the reproductive function switches off.

In other words, the central nervous system can interfere with the automatic realization of the reproductive function if the activity of the organism must be adapted to the demands of the external environment, but this control is not exerted unless required. Therefore, the hypothalamus functions to a large extent automatically, without supervision of the central nervous system, obeying only its own rhythm and signals from the body.

Alongside control of the reproductive system, the control panel for many other

functions is also located at the hypothalamic level. The hypothalamus regulates via the pituitary gland the growth of the body (growth hormone), the activity of the thyroid gland (thyrotropin) and the adrenal cortex (corticotropin), and the function of the mammary gland (prolactin, the hormone stimulating lactation). The hypothalamus and the adjoining sections of the brain contain the sleep centre, the centre controlling emotions, the centre of appetite, and the centre of heat production and thermoregulation.

The hypothalamus contains structures that are associated with the regulation of pleasure or delight. If the activity of certain structures in the hypothalamus is excited by electrical stimulation, the animal will seek repeated stimulation even if pain is inflicted during the pursuit.

Many of these centres function interdependently, e.g., the sections of the hypothalamus that control the appetite, emotions, and energy metabolism. The hypothalamus incorporates special structures, or centres that are associated with the regulation of cardiac activity, vascular tension, immunity, water and saline balance with the functions of the gastrointestinal tract, urination, and so on. And what is more, certain centres in the hypothalamus are directly related with the vegetative nervous system as a whole.

Unlike the central nervous system, the vegetative nervous system regulates the activity of the internal organs, or, to be more precise, controls the recurrent automatic processes in the body. The vegetative system itself consists of two parts: the sympathetic and parasympathetic systems, which exert opposite effects on the tissues and organs. For instance, if stimulation of the sympathetic system causes a rise in arterial pressure, stimulation of the parasympathetic system leads to a decrease. Thus, these two opposed and interacting parts of the nervous system stabilize, within certain limits, deviations in all the processes that are regulated by the vegetative nervous system. Therefore, when profound affection of the hypothalamus is induced experimentally in animals, trophic disorders develop in almost all the organs.

Appetite and growth, sleep and wakefulness, emotional excitation and mental depression, and, finally, reproduction are greatly dependent on the activity of the hypothalamus. There is no function in the complex integration of the organism that does not demand the participation of the hypothalamus, but on the whole, the functions of this organ can be divided into two groups.

First of all, the hypothalamus adapts the activity of the organism to the environmental conditions. In other words, if the

mechanical protection, which in higher organisms is provided by the skin, muscular and bone tissues, is excluded, it is the coordinating activity of the hypothalamus that protects the organism against the detrimental effects of the environment, i.e., it counteracts the factors that can cause death due to external conditions.

Secondly, the hypothalamus is the chief organ that maintains the constancy of the internal environment. Together with the regulated organs, the hypothalamus functions as a distinct closed system that ensures this constancy repetitive in conformity with the information received from the internal world of the organism. It closely controls the constant and regular processes that should proceed in cycles irrespective of the outside world. But it also adapts the organism to the pressure of the external environment.

In short, the hypothalamus is the principal integrator of information coming from the body, and at the same time it is the collector that gathers information from the environment.

Moreover, the hypothalamic and pituitary hormones affect not only the body, but also the brain, and, in particular, the spirit, as it would be said in olden times. The same hormones that control the secretion of milk (prolactin), the adrenal cortex (corticotropin), and the mobilization of

fat (lipotropic hormones) are subjected to biological transformations in the brain. As a result, substances of more simple structure separate from these hormones and influence memory and learning, the emotional character of events, the perception of pain—in other words, the decision-making processes of the brain. It is remarkable that some of these substances (endorphins) resemble morphine in their structure, and the rate of their formation can depend on the state of the metabolism in the organism. Thus, the ancient expression "A sound mind in a sound body" seems to have materialized today and is one of the conditions that supports the *stability of the internal environment* in the organism.

To see how this is accomplished, let's recall the cybernetic principle that ensures *stability* in a system, no matter whether the system is a simple thermostat or the complex system of a living organism. The stability in a system is supported by a negative feedback mechanism. Let's examine how this mechanism functions. Assume that there is an endocrine gland A that secretes its specific hormone A_1 into the blood (Fig. 3). This hormone affects the cells that are sensitive to it in corresponding tissues (the target-tissues) and therefore it can be designated as a working hormone. Imagine a situation where there

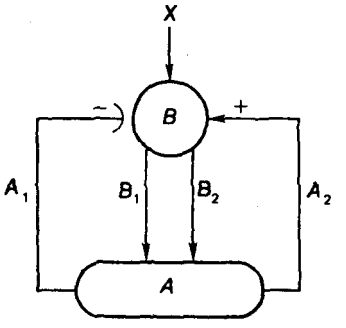

Fig. 3. Principle of feedback mechanism in endocrine system: B—regulator-gland; A—working gland; B_1 and B_2—regulating hormones; A_1 and A_2—working hormones.

Mechanism of negative feedback: at an increase of the activity of gland A the concentration of the working hormone A_1 increases, thereby inhibiting the activity of regulator B which, in turn, causes a decrease in the concentration of regulating hormone B_1 and a decrease of gland A activity, respectively.

Mechanism of positive feedback: an increase of the intensity of signal X causes an increase of regulator B activity, which increases the level of regulating hormone B_2, and, in turn, increases working hormone A_2 level. The latter causes further stimulation of regulator B_1 activity, and so on.

is an increase in the utilization of the working hormone and, as a result, its content in the blood decreases. To restore constancy in the internal environment it is necessary to enhance the activity of gland A. What happens in this case?

Gland A does not exist in the organism in an isolated form: it exists within a specific system of interrelations under the control of its regulator, which we'll call gland B. Gland B secretes hormone B_1, that controls the activity of gland A. It is this regulator-gland that perceives a decrease in the concentration of the working hormone A_1. When the content of the working hormone in the blood is constant, gland B does not respond: the receptors of its cells are sufficiently saturated with hormone A_1. But when the concentration of hormone A_1 has decreased, these receptors are partially freed of the working hormone. The inhibiting effect of the working hormone A_1 on the production of the regulating hormone B_1 ceases; therefore, gland B sends its envoy to gland A, viz., hormone B_1, to stimulate gland A. The production of hormone A_1 increases. When the concentration of the working hormone A_1 increases to the normal level, it fills the required number of free receptors on the membranes of the cells of regulating gland B. This is the signal to cease stimulating gland A: the constancy of the internal environment has been restored (here it is the concentration of hormone A_1 in the blood). As a result, there is a decrease in the stimulation of the working gland by the regulator and equilibrium is established. When the concentration of the

working hormone in the blood decreases once again, inhibition of the regulating gland ceases. The concentration of the regulating hormone again increases, and the activity of the working gland is enhanced once more, thereby supporting equilibrium.

The relationship described above, wherein the working hormone inhibits its regulator, is a typical example of negative feedback. The word "negative" in this cybernetic sense means that the regulator is inhibited by the action of the peripheral factor (the working hormone in this case) while the removal of the "negative" inhibitory effect stimulates the peripheral link in the system, viz., the working endocrine gland. This is the essence of the mechanism of negative feedback.

A similar principle of regulation is characteristic of any self-regulating system, for example, even in devices that maintain constant temperature in a thermostat.

The systems of the hypothalamus that support constancy of the internal environment are strictly regulated by negative feedback. This mechanism ensures observance of the law of constancy of the internal environment in the organism.

Certainly, one should not think that stability is something immobile and rigid. It is maintained by the active work of each individual system and of the organism

as a whole, which means that stability implies averaged fluctuations in each phenomenon, i.e., a dynamic equilibrium that is attained given the correct functioning of the homeostatic systems. At the same time, if stability is a necessary condition for the normal life of an organism, then any constant violation of stability should be considered a disease.

Frequently, in medicine exact definitions of basic notions do not exist owing to the complexity of the phenomena. Then, strange as it may seem, there is no exact definition of the term "disease". Regarding pathologic processes associated with violation of the constancy of the internal environment and regulation as a whole, a disease, by definition (i.e., in a strictly theoretical sense), is a persistent deviation from stability. In other words, any persistent violation of homeostasis is a disease because a disease is defined as any process in the organism that increases the probability of death. That this definition is correct not only in form, but also in essence follows from data on the role of stress in the origin of a particular group of diseases, the so-called adaptation diseases.

Chapter 2

Stress and Diseases

> Evolution, which formed the higher organisms, established that it is better to live the lifespan of the species and to die old and sick, than to die young and healthy at any moment owing to external environmental factors. Therefore, it is more correct to say that civilization does not cause the diseases of civilization but introduces a principle of uncertainty into the "programmed" mechanism of disease formation.

A series of stereotypical adaptational reactions aimed at the protection of the organism originates in the latter in response to any change in the conditions, which demands an increase in the organism's efficiency. Hans Selye, the well-known physiologist, defined the totality of these protective reactions as a general adaptation syndrome.

A rise or drop in the ambient temperature, hunger or thirst, loss of blood or physical exertion, infection or trauma, emotional tension or stupor—all cause certain changes in the organism that are combined in the concept "state of stress".

It seems that the organism in this case is not interested in the specific features of each stress factor, but reacts to the damaging factor as a whole. The stress reaction is especially advantageous for an organism because it is stereotypical, i.e., the organism can immediately start to protect itself

using one stereotypical reaction in response to a variety of extraordinary stimuli, or stress factors. The adaptation reaction is apparently the most vigilant guard of the organism because it always switches on automatically without the involvement of consciousness and only under the influence of unconditioned reflexes, pain, or a change in the composition of the internal environment (for instance, in the case of haemorrhage, a decrease in the blood sugar concentration due to starvation, etc.).

Artificial violation of the adaptational system causes most severe consequences for the organism. Thus, if the adrenal glands are removed from an animal, which results in failure of the stress reaction, then even under ideal conditions of care and nutrition, the life of an animal can be preserved only by the continuous injection of adrenal hormones. And when a stressful situation arises, the dose of these hormones must be sharply increased because otherwise the animal perishes due to insufficiency of the protection system.

And yet in natural conditions it is quite frequent that the organism pays a high price for its ability to protect itself by adaptation. A large group of diseases, so-called adaptation diseases, are a consequence of stress.

Let's discuss the classical example of an encounter between a cat and a dog analyzed

from the physiological point of view by Walter Cannon, who is the author of the term "homeostasis". We'll supplement this example with the description of a stress reaction in the spirit of Hans Selye and shall include some additional details uncovered by numerous researchers of stress after the fundamental works of Selye. Finally, we'll introduce an important element into the description of this situation that was missed by Selye, viz., an elevation in the hypothalamic threshold of sensitivity to the regulatory signals. Without an elevation in the hypothalamic threshold no stress reaction of any significant duration occurs. It is true, however, that the cost of adaptation to the organism would not be so high, given a lack of elevation in the threshold.

To continue, the dog and cat meet. Even at a distance, the sense organs send signals to the central nervous system informing it that the enemy is near. There will possibly be a fight and it is necessary to prepare for it. The situation is evaluated by the cerebral cortex, but it has an emotional character.

It is precisely the emotion that is one of the strongest mobilizing factors. The control of emotions is concentrated mainly in the hypothalamus. When the cat adopts the characteristic pose with an arched back, it means that the information received from

the cerebral cortex excited the emotions of fear and aggression in the hypothalamus. This is the phase of preparing for a fight. The animal's emotional pose per se sets the body into a state of readiness for immediate motion.

Simultaneously, the hypothalamus sends signals to the vegetative nervous system, to the part that controls the functioning of the internal organs. This signal rapidly reaches the adrenal glands and they secrete the hormone, adrenaline. This is easily visible externally because adrenaline causes contraction of particular muscles of the skin and the animal's hair stands on end. The discharge of adrenaline into the blood contributes to dilatation of the vessels of the heart, brain, and lungs, and, in contrast, causes constriction of the vessels of the skin and internal organs, especially, the digestive organs. Owing to the latter, a redistribution in the blood volume, which is useful for the fight, occurs. The cardiac activity is enhanced and the arterial pressure rises.

All this activity requires a supply of energy and adrenaline mobilizes both sources of energy—fatty acids from the fat depots and glucose from the liver—thereby increasing the nutritional supply of the muscular tissue and brain. These responses taken together, viz., dilatation of the skin vessels, hair standing on end, that reduces

heat transfer, increase in the fatty acid and glucose levels of the blood, and light trembling, contribute to a rise in the body temperature, thereby creating optimal conditions for chemical reactions. This resembles the warming-up of a sportsman before the start, and occurs within several seconds.

Finally, adrenaline sharply increases the ability of the heart to assimilate oxygen. (It should be noted that this protective measure can be very dangerous for a human. Thus, too intensive absorption of oxygen from the blood by the heart, which may be induced by negative emotions, can create temporary oxygen deficiency that sometimes causes cardiac insufficiency and even myocardial infarction. In case of a normal stress reaction, however, the adrenaline is rapidly destroyed after stimulating the further development of antistress protection.)

By this time, in the hypothalamus changes occur in the concentration of the hormonal mediators that transmit neuronal signals, i.e., neuromediators. The consumption of these substances increases during the stressful situation as they activate the hypothalamic centres controlling the secretion of corticotropin, growth hormone, and prolactin from the pituitary gland into the blood. These hormones have a pronounced ability to mobilize fatty acids

from fat depots. This effect is energetically necessary but adrenaline should not be used for a long time to this end because it causes an autonomic storm that is too severe. If the situation that has caused the stress is not of short duration, then a transition to a more solid energy base is necessary, which is ensured by putting into action the fat-mobilizing hormones of the pituitary gland: corticotropin, growth hormone, and prolactin. These hormones take fatty acids from the fat depots that supply the heart with six times more energy than glucose.

The hypothalamic corticotropin-releasing hormone (CRH), on the one hand, stimulates the sympathetic nervous system and, as a result, increases the content of the stress hormone, norepinephrine, in the blood; on the other hand, it involves the pituitary hormone, corticotropin, which controls the activity of the adrenal cortex in supporting the stress reaction. The adrenal cortex is always activated when protection is necessary. At first, the hypothalamus activates the medullary layer of the adrenal glands by purely nervous impulses, causing the secretion of adrenaline. Then corticotropin stimulates the secretion of protective hormones from the adrenal cortex, among which the main one is cortisol. Cortisol possesses many properties characteristic of adrenaline but it has a more

powerful effect. A second transformation of the signal seems to occur, i.e., at first the nerve signal is transformed into a hormonal one (the discharge of norepinephrine and adrenaline in response to activation of the hypothalamus), and then the hormonal response is transformed into a long-term endocrine protection reaction.

In particular, cortisol (especially in combination with growth hormone) decreases the utilization of glucose by muscular tissue. This is very important as the muscles splendidly utilize fatty acids, while the nerve cells need glucose which is the main fuel that they assimilate. Cortisol also affects the redistribution of "fuel" in another way, viz., it activates the process of transforming certain amino acids into glucose. This is very important because during a fight there is no external food supply and the reserves of sugar in the organism—glycogen—are quite limited. (It should be noted here that it is precisely for this reason that the secretion of a large amount of cortisol induced by very powerful emotional stimuli may even induce temporary diabetes mellitus in a human because of the inability to rapidly assimilate the newly formed glucose. Long-term stress may cause permanent diabetes mellitus if an individual has a predisposition to this illness.)

It should be noted here once again that proteins are structural and functional elements of cells; therefore, the transformation of cellular proteins into sugar is highly disadvantageous for the organism. Consequently, if it is necessary to burn complex proteins, with their numerous properties, as simple fuel, then it is better to take the proteins from tissues that are rapidly renewed in the organism and, more importantly, that have no specific structural function so that a temporary decrease in the mass of this tissue will not be so damaging. Such tissue is represented by lymphocytes, which are distributed in the lymphatic glands and other lymphoid tissues, viz., the spleen, bone marrow, and, finally, the thymus, an organ controlling immunity.

Many of us know that it is easy to fall ill with a catarrhal, viral disease after an intense and lengthy period of anxiety. One might wonder what could there be in common between anxiety and the susceptibility to infection? Nevertheless, this susceptibility is conditioned, in particular, by utilization of the amino acids of destroyed lymphocytes to supply the energy requirements of the organism during stress (Chapter 9).

But all these remote consequences are not taken into consideration at the height of the stress. On the contrary, the supply of energy is the most important problem.

Additional nutrition must be supplied rapidly to the tissues, and the hypothalamus transmits impulses to the motor nerves of the heart and vessels. The lumen of the vessels of the internal organs constricts still more, the activity of the heart is intensified, the blood pressure rises, and, as a result, the blood circulation accelerates. (This is the reason why intense negative emotions are most dangerous for a person suffering from hypertension. They are also a threat for healthy humans because they contribute to the incidence of hypertension.*)

Simultaneously, adrenaline, growth hormone, fatty acids, cholesterol, cortisol, etc.—all the factors that are involved consecutively in supporting the stress reaction—increase the coagulability of the blood, thereby assisting to avoid heavy bleeding in case of wounds. (But the same

* The ideas of G. Lang, an outstanding clinician, allow hypertension to be viewed as an adaptation disease. But in the course of aging the number of hypertensives increases and the level of arterial pressure rises in normotensives. This indicates that, as in the case of other hypothalamic systems (see Chapters 4 to 7), there is an elevation in the hypothalamic threshold to signals aimed at the stabilization of arterial pressure. In other words, hypertension is simultaneously an adaptation disease and a normal disease (see below). However, there is a large group of hypertensions caused by other factors, e.g., renal or hormonal (so-called symptomatic hypertensions).

protective mechanism can be the cause of thrombosis of the vessels and myocardial infarct in humans under the influence of emotional excitation.)

During the fight everything that hinders stress reaction should be inhibited. Therefore, cortisol during this critical situation serves to supply energy, contributing, in particular, to the synthesis of carbohydrates from protein, and not only suppresses the reactions of cellular immunity, but is also capable of suppressing inflammation, thereby reducing the degree of impairment of the tissues in case of trauma. (It is for this reason that cortisol and its derivatives, cortisone, prednisolone, etc., have found such successful application in modern medicine for various inflammatory processes, beginning with inflammation of the iris of the eye (iritis) and including ulcerative colitis, rheumatism, diseases of the joints, and myocarditis.)

But if the tissue impairment is great, then some of the proteins from the traumatized tissues enter the bloodstream, reach the immune system, and, acting on it like "foreign" proteins, effect immunization against the body's own tissue proteins. In this case the "carriers of immunity", the antibodies, may impair the tissues while penetrating into the latter. This threatens the animal with diseases or even death at some time after the fight is over

because of auto-immune diseases, which develop according to the same laws that make up incompatibility of tissues an obstacle in transplantation of "foreign" organs from one human to another. Therefore, cortisol, which supplies the organism with energy at the cost of the destruction of the lymphocytes, reduces immunity in the course of the stress and weakens the threat of immunization against its own tissues. (Correspondingly, owing to its ability to suppress immunity, cortisol has found wide application in curing allergic states, such as bronchial asthma.)

Cortisol and the regulator of its production, corticotropin, as well as prolactin have the ability to inhibit the activity of the "sex centre" in the hypothalamus. This is biologically expedient because while the fight has not yet come to an end and its outcome is uncertain the wounded animal should have no offspring. (Thus, it is not infrequent that women experience cessation of the menstrual cycle after prolonged negative emotions, while men experience decreased sexual potency.)

Stress, which eliminates everything extra, also suppresses the appetite. The hypothalamic appetite centre is inhibited during emotional excitation just like the activity of the digestive system. This is expedient during a fight. (One of the signs of this known to everyone is the drying of

the mucous membrane in the mouth and throat when one gets nervous.)

Finally, the fight that required a great expense of energy comes to an end. The phase of recovery commences.

The hypothalamus enhances heat transfer via the thermoregulatory centre. The skin vessels dilate, perspiration increases, and dogs, which have no sweat glands, experience dyspnoea and their tongues nearly fall out to increase evaporation. All this protects the organism against excessive superheating, which may occur because of intensive burning of fatty acids and glucose during the fight.

The excess of fatty acids, whose intensive mobilization was so necessary, serves during recovery as the raw material for the synthesis of cholesterol. This circumstance is very important because "repair" of the impaired tissues by cell division is necessary during the poststress period. At the same time, each new cell requires a membrane whose structure contains a lot of cholesterol. Thus, a metabolic shift during stress towards enhanced utilization of fatty acids is intended not only to satisfy the energy requirements but also to save and recover the reserves of glucose. This metabolic shift also ensures suppression of immunity, an increase in blood coagulation, and, the production of cholesterol, which is necessary for cellular division.

All these changes take place during each emotional stress. For instance, the content of cholesterol in the blood, which is one of the main factors in the development of atherosclerosis, increases in students when they are taking their examinations. But life makes it necessary to pass exams not only within the walls of the alma mater. Thus, frequent and prolonged nervousness, which creates a stress reaction, induces the development and progression of atherosclerosis.

But all the negative consequences of stress are seemingly in the future, while now, during the phase of immediate recovery, everything described above is advantageous. A special antidiuretic hormone—vasopressin—enters the pituitary gland directly from the hypothalamus and then enters the bloodstream, delaying the renal elimination of water and thereby assisting in the recovery of blood losses. The functioning of the thyroid gland, whose hormones are necessary for the repair of damaged tissues and which was inhibited earlier by the hypothalamus, is amplified. This occurs because the hypothalamic centre that regulates the activity of the thyroid gland inhibits the latter's activity at the beginning of the fight and then stimulates it when the period of recovery commences. The secretion of cortisol attenuates, which contributes to the recovery of protein syn-

thesis, while earlier cortisol had hindered the synthesis by transforming protein into sugar.

Thus, the protection mechanism is regulated via the hypothalamus, stage by stage, followed by the reversal of the damage if the latter was inflicted by the external environment but was still compatible with life.

We have discussed how the stress reaction ensures protection of the organism during a vitally dangerous time. But let's recall how the mechanism of protection against stress was realized. There was an increase in many hormones in the blood, viz., adrenaline, growth hormone, prolactin, corticotropin, and cortisol; the concentration of many substances that supply the organism with energy increased in the blood, viz., fatty acids and glucose; cholesterol accumulated; the coagulation of blood was amplified; the arterial pressure went up, etc. All this indicates a deviation from the law of constancy of the internal environment, a law whose observation as well as protection is necessary for life itself.

However, we know that homeostatic systems strive for the recovery of stability owing to the cybernetic mechanism of regulation. The following question is quite reasonable: how can violation of the internal environment of the organism continue throughout the entire stress situation, i.e., while "the cat is confronting the dog"?

Indeed, if the concentration of the working hormone, e.g., cortisol, increases in the blood, then, in conformity with the mechanism of negative feedback, it should inhibit the secretion of its regulator, in this case, the pituitary hormone, corticotropin. At the same time the secretion of cortisol, which is not stimulated by corticotropin, should drop to average levels, i.e., to those protected by the law of constancy. But the latter does not occur and the level of cortisol in the blood during the period of stress remains increased, thereby creating a mechanism of antistress protection. How can this be explained?

There is a working factor for each regulator-hormone, which suppresses the activity of the latter when the concentration of the regulator-hormone increases in the blood. The secretion of corticotropin should be inhibited by an elevated level of cortisol; the growth hormone and prolactin, by an elevated level of sugar and fatty acids. And yet, a high concentration of regulator-hormones, working hormones and energy substrates are found simultaneously in the blood during stress.

As was mentioned above, when Selye discussed the increase in the activity of the pituitary gland and hypothalamus during stress, he paid no attention to the fact that an increase in this activity cannot exist for any long period of time if there

is no increase in the sensitivity threshold of the hypothalamus to the inhibiting effect of peripheral signals.

The mechanism controlling the increase in hypothalamic threshold has great physiological significance. In its absence the stress reaction would be short, i.e., it would continue as long as it would be necessary for negative feedback to begin operating, which would bring the protective system to equilibrium, thereby depriving the organism of protection. As we know, this does not occur, which indicates that during stress there really is an increase in the hypothalamic threshold to regulatory signals. Therefore, during the action of the stress factors on the organism, the hormonal-metabolic shifts are preserved, viz., a rise in the concentration of glucose in the blood, as well as fatty acids, growth hormone, cortisol, and so on.

The latter makes it possible to explain many things in the relationship between stress and diseases that are caused by a disturbance in homeostasis. In other words, the fact that higher organisms are equipped with such a high capacity for protection against stress is conditioned by the evolution of complex homeostatic systems, which are crowned by the hypothalamic systems. These systems ensure that homeostasis can be disturbed, which is necessary for the protection of the organism.

But the inevitable disturbance in homeostasis causes diseases that Selye called adaptation diseases. In this way, the organism pays a high fare for protecting itself from external causes of death. Thus, adversities and sorrows reduce the life-span.

It remains to be added that the increase in hypothalamic threshold during stress occurs as follows: when the cat and the dog notice one another, the signals, evaluating this event, rush from the central nervous system to the limbic system and the hypothalamus, thereby stimulating the activity of the latter. As a result, the consumption of the neuromediators increases. As we know, the vegetative nervous system is divided into the sympathetic and parasympathetic systems. Correspondingly, there are S-mediators for sympathetic impulses and P-mediators for parasympathetic impulses.

The group of S-mediators includes dopamine and norepinephrine, substances that are structurally similar to adrenaline, the hormone of fear. The group of P-mediators includes serotonin and compounds similar to it. S- and P-mediators are synthesized from the amino acids, tyrosine and tryptophan, respectively. A decrease in the concentration of S- and P-mediators in the hypothalamus during stress due to their increased consumption causes an increase in the hypothalamic threshold. Mental

depression commences if the decrease in the concentration is too great.

It is well known that apathy may set in for some time after a period of excessive emotional excitation. It is symptomatic of exhaustion of the neuromediator reserves, a warning that rest is necessary for recovery. Indeed, the concentration of mediators in the hypothalamus normalizes at a rate that is greatly dependent on the natural strength of the nervous system, i.e., on its specific genetic and metabolic features. The hypothalamic sensitivity threshold is reestablished and the system of self-regulation again begins to function properly, ensuring a constant internal environment in the organism. The storm that blew over together with the stress abates, the past is forgotten or almost so if the activity of the organism during the stress was not so seriously disturbed.

This appeasement after the storm represents the difference between stress and everything that is associated with aging, wherein pathologic processes develop gradually and inevitably, even without the participation of external factors. Therefore, in the following chapters let us consider the reason why such perfect homeostatic systems in higher organisms, which can independently resist the effects of intense stress and relatively rapidly recover equilibrium in the organism, are unable

to maintain stability of the homeostasis in the process of aging. Certainly, it is logical to assume that homeostatic systems *simply "break down" in the course of time*, in particular, under the influence of various external and internal damaging factors. These views will be discussed in the section dealing with aging (Chapter 11). The following chapter will present arguments that support quite a different point of view, viz., the fact that a disturbance in homeostasis is a necessary element in the development of the organism and becomes the key element in aging when growth and sexual maturation finish.

Chapter 3

The Law of Deviation of Homeostasis

> If the stability of the internal environment is a *binding* condition for the life of the organism, then the programmed disturbance of this stability is an indispensable condition for the development of the organism. Correspondingly, there is a law of deviation of homeostasis alongside the law of constancy of the internal environment.

A living organism is in constant relationship with the external world. The availability or lack of food, the physical conditions of the environment, the degree of its pollution—these are the principal factors that are inextricably bound with the vital activity of the organism.

At the same time, an organism can exist only on condition that the composition and functioning of its body is maintained within certain, usually quite narrow, limits. Claude Bernard, a great French physiologist, formulated this thesis more than 100 years ago as follows: constancy of the internal environment is a necessary condition for the life of an organism.

The maintenance of the internal environment in an organism is a fundamental law of biology. I would even designate it as the First fundamental law, though the ordinal number carries little significance

because all the fundamental laws are characterized by the fact that neither one of them can be violated. Let's discuss the following example.

In theory, certain unicellular organisms are immortal because each division of these creatures is followed by the emergence of two absolutely identical descendants. The process of successive division can continue without limit if the conditions are favourable. A classical example is the division of the unicell paramecium in the course of 8400 generations. It is of no importance in this case that in reality only representatives of the simplest organisms create generations that can propagate vegetatively (asexual reproduction) for an indefinite period of time. If this capacity were observed in only one species of protozoans, or even one branch, then even this would provide grounds for asserting that in theory, under certain favourable external conditions, life can exist without internal causes of death.

Nevertheless, unicells do perish. Indeed, it was calculated long ago that if they did not perish, then the progeny of one infusorian would very soon occupy a volume exceeding that of the globe. The homeostatic mechanisms in unicells are not perfect owing to the insufficient complexity of the organism's structure. Therefore, death from external causes became an in-

surmountable obstacle for unicells to theoretically eternal life.

During evolution of unicells into multicellular organisms mechanisms developed for the maintenance of a constant internal environment by specialization of the body organs. This, however, also led to an irreconcilable contradiction between the requirements for development and the necessity for stability, a contradiction that may have resulted, during evolution, in a regulatory type of death owing to internal causes (see Chapter 11).

Indeed, the law of constancy of the internal environment, which is protected by homeostatic systems, should be observed at any given moment of development and growth in the multicellular organism. At the same time, it is quite apparent that the capacity of the homeostatic systems themselves must increase in the course of development in order to meet the organism's requirements for growth. In other words, the development and growth of the organism would be unrealizable if not for a simultaneous increase in the capacity of the homeostatic systems. In a certain sense, development is an increase in the capacity of homeostatic systems. Hence, if life is possible only under the condition that the internal environment is stable, then development and growth are impossible without disturbance of this stability.

This thesis can also be expressed as follows: in higher organisms it is necessary to combine the states of rest and motion, i.e., rest of the internal environment, which ensures stability of the organism, and motion, which promotes development.

It can be assumed that this combination of absolutely opposite requirements is realized through the self-development of the homeostatic systems. In other words, systems ensuring stability must continuously develop, thereby increasing their capacity, and only in this case it is possible to preserve regulation in a moving system.

But how can a disturbance in homeostasis, which is necessary for development, be ensured if it is protected by the law of constancy of the internal environment? It will be seen in the examples below that disturbance in homeostasis is achieved in all the representatives of the class of Mammalia by one and the same pathway, although the mechanisms of the homeostatic disturbance are different during the intrauterine and postnatal development of the organism.

Numerous changes occur in the organism of a pregnant woman: the content of fat increases, especially in the second half of pregnancy; the size of the nose and chin increases owing to swelling of the soft tissues in the face. At the same time, the concentration of sugar and cholesterol increases

in the blood. Sometimes the sugar level is so high that doctors call it "diabetes". In other words, the law of constancy of the internal environment is disturbed during pregnancy and, in essence, certain diseases develop if it is borne in mind that any stable homeostatic disturbance is a disease.

The following question is quite justified: can such a vitally necessary phenomenon as pregnancy be accompanied by diseases, especially if it is taken into consideration that all the harmful properties would have long ago been eliminated by natural selection during evolution? It is logical to assume that if the elimination of diseases has not occurred then homeostatic disturbances during pregnancy are extremely necessary. Let's see what purposes these disturbances can serve.

An organism has two sources of energy, viz., glucose and fatty acids. The utilization of these energy substrates is regulated by special mechanisms. For example, fatty acids are the main fuel during the night when there is no intake of food. But the use of fatty acids reduces the consumption of glucose by the muscular tissue, which serves to preserve the glucose stores during the period of nocturnal starvation. As a result, the glucose can be used to supply the cells of the nervous system with energy. Furthermore, the glucose that is saved from

consumption in the organism of a pregnant woman is supplied to the fetus, for which it is actually the only source of energy. Finally, fat is synthesized from the fatty acids and products of glucose metabolism in the mother's liver and adipose tissue, owing to which obesity, which is so typical of pregnancy, develops.

When the amount of fat in the organism increases, an abundant amount of fatty acids enters the blood from the fat depots. Therefore, an increase in the concentration of fatty acids, which inhibits the use of glucose by the tissues, leads to a farther increase in the concentration of glucose in the blood after a meal. A phenomenon arises which is characteristic of latent diabetes mellitus. During this period, fatty acids are the basic source of energy in the organism of a pregnant woman. But only a limited amount of fatty acids can be supplied through the placental barrier, which protects the cells of the fetus against potential toxic effects associated with the intensive utilization of fatty acids. At the same time, an increased amount of cholesterol, an inherent structural element of each cell, is produced in the maternal organism from the products of fatty acid metabolism.

Cholesterol is part of the framework of the cell membrane. The majority of cell types are unable to independently synthesize the amount that is necessary to build

the cell membrane, and, thus, they receive cholesterol synthesized by the liver. The capacity of the fetus' liver is still small: it does not satisfy the requirements of the rapidly growing cell mass; therefore, cholesterol must be supplied from the maternal organism. But this source of cholesterol is also quite limited. After all, the law of constancy of the internal environment is specifically intended to protect the organism against a shortage or an abundance of a metabolite. For this reason, the law of constancy must be breached: the fetus' developmental requirements for cholesterol must be met.

An essential characteristic of this homeostatic disturbance is the fact that the mechanism changing the homeostasis is located in the placenta, which is a temporary organ. During pregnancy the placenta produces a series of hormones, one of which is the placental growth hormone, which reduces the utilization of glucose in the maternal organism. Furthermore, the placenta is not a permanent part of the neuro-endocrine system, and it is not included in the system of self-regulation that restrains the activity of other endocrine glands by the cybernetic negative feedback mechanism. Therefore, the production of placental hormones increases practically up to the end of pregnancy paralleling the increase in the size of the placenta. Thus, the disturbance

in homeostasis is maintained during the entire term of pregnancy; however, the homeostatic changes that are characteristic of the term of pregnancy are temporary because the existence of the placenta comes to an end with childbirth. The shifts in metabolism that contribute to the onset of diseases are also eliminated.

In light of that stated above it is possible to understand what purpose these metabolic disturbances serve, being manifested in extreme cases in pregnancy-induced diabetes mellitus, i.e., in essence, in a "planned" disease. All these changes are necessary for the material support of the fetal development program. This biological task can be fulfilled only by disturbing the homeostasis. It is clear that diabetes mellitus in this situation is a by-product of mechanisms that are necessary for the realization of the principal task, i.e., the reproduction.

The changes described are not only confined to the class Mammalia. They are manifested most vividly in some species that are quite remote from mammals, in particular, in the Pacific salmon. This fish lives in the Pacific Ocean for four to five years after hatching from fertilized eggs in the mouths of Far East rivers. During this period the fish matures, its size increases, and it accumulates fat. But when the period of reproduction approaches, the fish begins its

long journey, sometimes extending over thousands of kilometres, to the mouth of the river where it was born. From the very beginning of this journey the fish uses mainly its fat reserves as the source of energy. The store of fat reduces but the concentration of cholesterol in the blood, which is synthesized from the fat, increases. The fish "grows old" within one to two months: its jaws bend, the eyes sink in, the skin becomes thin. Comprehensive shifts take place in the fish's organism with signs characteristic of diabetes mellitus and atherosclerosis appearing. The salmon's resistance to *infections* weakens. Finally, the female deposits eggs to be fertilized by the male. The parent-fish dies one or two weeks later. The causes of death are numerous infarctions of the heart, brain, lungs, and kidneys. The reason is clear: the concentration of cholesterol in the blood of a Pacific salmon during spawning increases up to 1000 mg%, i.e., approximately tenfold. All the fish die: no representatives of this species return to the ocean after spawning.

The mechanism of death of the Pacific salmon is a typical example of death due to internal causes, which also gives the impression that there is such a thing as programmed death. The life of the fish seems to end in conformity with a program stored in the genes, as if a "stop" signal is encoded there.

But let's ponder over this: by acknowledging the correctness of this conclusion, we are acknowledging that nature has a goal, which is the death of the individual after the end of reproduction. However, it can be asserted quite definitely that nature has no such goal, and what is more, it cannot have such a goal (see Chapter 11).

How can these mutually incompatible theses be combined? In reality, what is recorded in the genetic code of an organism is the reproduction of ones similar to oneself. This process must be materially supported. Apparently, owing to certain conditions of the habitat, the majority of sex cells in the Pacific salmon perish after it spawns without being fertilized. But the capacity to produce a large quantity of sex cells mollifies the action of this factor which is unfavourable for reproduction.

What is the reason for the accumulation of fat in the liver and in the "hump" if the Pacific salmon is destined to die soon after spawning? The point is that cholesterol is formed from the fat and each sex cell contains a large amount of cholesterol. This cholesterol is the material used for building the membranes of the sex cells that develop into a complex organism after fertilization. But at the same time, an increase in the cholesterol content of the blood affects the vessels and, in the end, leads to the death of the organism. Thus,

in essence, the surplus cholesterol in the blood supports the process of reproduction, while the death of the salmon is only a collateral consequence caused by a disturbance in the constancy of the organism's internal environment.

From this point of view, the death of the Pacific salmon is a particular example of death due to disturbances in the system of self-regulation. The particular significance of this example lies in the fact that the changes in the system of self-regulation, which result in an increased production of cholesterol, are induced by signals from the sex glands, i.e., the death mechanism switches on in accordance with the requirements of the reproduction program. But the sexual function is also switched on due to the more intensive work of the self-regulating system, which, on the one hand, satisfies the requirements of reproduction, and, on the other, turns into an instrument that brings about the death of the organism due to internal causes. Thus, death due to internal causes, which is characteristic of highly organized living systems, is a result of the interaction between the mechanisms of development and stabilization that are protected by the law of constancy of the homeostasis.

But if deviation of homeostasis is really a necessary condition for the development and growth of the organism, then how can

this deviation be realized in mammals, in particular in a human during the development and growth of the child after its birth?

Healthy children usually appear stout during their early life. Many ancient sculptures and paintings immortalized this peculiarity. This is in fact a manifestation of the same thesis, viz., development requires additional energy, which is derived from fat. In the given case the pleasant stoutness of the child reflects the disturbance in the constancy of the internal environment.

And it cannot be otherwise. Growth (of the fetus and then of the child) is associated with the emergence of new cells, and they, in particular, need additional cholesterol, which in its turn, is synthesized when the utilization of fat increases.

But how is an increase in the capacity of the homeostatic system, which is protected by the law of constancy of the internal environment, ensured?

A study of this problem leads to the conclusion that the law of deviation of homeostasis does not extend to all the regulated functions of a living organism; rather it applies to only three of them. But these three functions control the three basic properties of a living organism.

What distinguishes a living system from a nonliving one is the capacity to reproduce, adapt and regulate the flow of energy

(or metabolism). Metabolism, which ensures maintenance of the energy processes, is the main one of the three basic properties of a living system. In the final end, a living system is an energy-converting machine running on fuel—food—to maintain its structure and activity.

At the same time, the activity of a living system is significantly subordinated to the requirements for adaptation to the changing conditions of the organism's external and internal environment. The greater the capacity for adaptation, the greater the vitality of the system. It is quite natural that the energy processes also lie at the base of adaptation (see Chapter 4).

Finally, the capacity for reproduction is the property that ensures the continuation of the species. Reproduction is also supported by the activity of the energy system. An extreme variant of such support is provided by the example of the Pacific salmon's mechanism of natural death.

These three basic properties of a living system are characterized by close interaction. But they are also united by the requirements set by the developing organism. An increase in body size, intensification of protective functions, and maturation of reproductive capacity vividly characterize the increase in the capacity of the energy, adaptational and sexual (reproductive) systems as the organism develops.

The three properties of a living system need structural organization, i.e., a certain mechanism that would permit them to manifest themselves in an organism. Correspondingly, each complex organism incorporates an energy, an adaptational, and a reproductive system that can be designated as an energy, adaptational, and reproductive homeostat*.

Unlike classical cybernetic systems, which are usually designed to maintain constancy in the controlled system, self-development takes place in the energy, adaptational and reproductive homeostat, increasing the capacity of these systems in conformity with the requirements of the developing organism. Therefore, it would be correct to call self-developing homeostatic systems as dynamic-cybernetic systems.

For instance, to maintain constant temperature in one or the other system, the sensitivity of the regulator to the varying temperature must be kept constant. Indeed, when the temperature in the thermostat reaches its predetermined limit, a sig-

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* The term "homeostat" sounds and, to a certain extent, is similar in meaning to the term "thermostat". As in the case of a thermostat, which is designed to maintain a certain temperature, the energy, adaptational and reproductive homeostat contains a mechanism for the regulation of the corresponding property, or function. But this regulation is specific.

nal is transmitted to the regulator to switch off the heating system.

But let's imagine that the sensitivity of the regulator to the temperature gradually drops in time. This inevitably leads to heating of the thermostat to a higher temperature until the regulator is acted upon to switch off the thermal element. If the sensitivity of the regulator continues to drop, even slowly, the thermostat heats up more and more. In other words, the thermal output of the thermostat, or its capacity, increases.

Thus, the difference in the principle of regulation between classical and dynamic-cybernetic systems is that the sensitivity of the regulator in the latter changes. If the mechanism of cybernetic regulation is preserved, it leads to, in the final end, a disturbance in stability, i.e., a deviation of homeostasis.

This change in the sensitivity "set point" of the hypothalamus, which controls the three basic truths of homeostasis, in reality exists. It is observed most clearly in the mechanism of age-related engagement of the reproductive function (Chapter 5).

Thus, alongside the mechanism that maintains equilibrium and constancy (homeostasis) at each given moment, there is a mechanism that ensures disturbance of the homeostasis over time, thereby realizing the developmental program of the organ-

ism. And, if stability of the organism's internal environment is the organism's law of existence, then programmed disturbance of the homeostasis is the organism's law of development. Therefore, the law of deviation of homeostasis coexists with the law of constancy of the internal environment.

However, a skeptic may ask: but what is new about the law of development? It was clear without it that, owing to the presence of a genetic program of development, a concrete mechanism ensuring this development should exist. But an answer to this seemingly simple question can be formulated only on the basis of the law named by the author as the law of deviation of homeostasis and, what is just as important, on the hypothalamic mechanism of realization of this law.

If only the law of constancy of the internal environment existed, then a number of exceptions would be necessary that would prohibit the action of this law under all the conditions arising during the organism's development, because development, as we have just elucidated, is always associated with a disturbance in equilibrium and stability. In other words, the law of constancy of the internal environment without its antipode—the law of deviation of homeostasis—should prohibit development. Consequently, the fundamental law of con-

stancy of the internal environment can exist only in dialectical unity with its opposite.

But this is not all. Both laws should be realized by similar rules (mechanisms) so that both opposed laws could coexist, ensuring both stability at each given moment, and the disturbance of stability over time. This condition can be satisfied only at the uniting, integral level of the hypothalamus where the three basic homeostatic systems meet.

In regard to how these two opposite functions are technically combined, the following can be assumed. Though the activity of the whole hypothalamus is directed toward realization of the law of constancy of the internal environment, the part of this activity that simultaneously serves the opposite law, i.e., the law of deviation of homeostasis, is as if isolated, forming a hypothalamic-pituitary complex. We mentioned earlier that the three basic properties of a living organism, i.e., the capacity to regulate the energy flux, adaptation and reproduction, should intensify during the organism's growth and development. Thus, the law of deviation of homeostasis is realized. But this increase in capacity is hardly possible only as a result of changes in the hypothalamus. The hypothalamus is made of nerve cells that lose the ability to divide at a mature age.

The anterior lobe of the pituitary gland, which is included in the hypothalamic-pituitary complex, is another matter. This part of the pituitary gland consists of glandular tissue, which is characterized by the ability to increase the working volume of each of its cells as well as the quantity of cells. Therefore, the capacity of the system can easily increase (on account of activity of the pituitary gland) and, at the same time, accurate regulation can be preserved in accordance with the hormonal signals from the nerve cells of the hypothalamus. As a result, the hypothalamic-pituitary complex is the "physical base" of a special type of regulation characteristic of dynamic-cybernetic systems of the energy, adaptational and reproductive homeostat.

But the hypothalamic-pituitary complex is not sufficient to increase the capacity of the latter three homeostats. It is clear that an unusual pathway for changing the regulation is necessary, for which the cybernetic principle, characteristic of all the systems of control, would transform into a dynamic-cybernetic one in conformity with the law of deviation of homeostasis.

This principle lies at the organism's basis of development. Hence, the law of constancy of the internal environment and the law of deviation of homeostasis are realized in the hypothalamus simultaneously.

But there is another property of the hypothalamus (as a part of the nervous system) that ensures realization of the law of deviation of homeostasis.

Each nerve cell is a miniature endocrine gland in that it produces substances that, in principle, are similar to typical hormones. As applied to the nervous system, these substances are called mediators, neurotransmitters, or neuromediators.

The nerve cells, strictly speaking, do not form a continuous circuit along which an electric impulse—a signal—would travel. Processes branch away from the body of each nerve cell and are arranged near the membrane of the adjacent nerve cell. Mediators are secreted from the process into the space, or cleft (synaptic cleft), between the nerve cells, which, like hormones, act on the membrane receptors of the adjacent nerve cell. They either stimulate or inhibit its activity. Each hypothalamic cell also has membrane receptors for the working hormones of endocrine glands. These hormones act on the hypothalamus through a feedback mechanism, by stimulating or inhibiting the activity of the hypothalamic cells.

Each one of the three basic homeostatic systems is represented as nuclei, or centres, in the hypothalamus. Special hypothalamic hormones are produced in the cells of these centres that control the release of each hor-

mone of the anterior pituitary. In their turn, the pituitary hormones and the hormones of the peripheral endocrine glands, i.e., the working hormones, effect the nerve cells that form these centres.

The structure of the hypothalamus ensures wide possibilities for changing the sensitivity threshold of this regulator. Indeed, the most simple method for changing the sensitivity threshold to the working hormones is to change the quantity of receptors on the cell membranes of the respective hypothalamic centre, e.g., "the sexual centre" of the reproductive system. If there are fewer receptors, then fewer molecules of the working hormone interact with the membrane of the nerve cell and correspondingly the sensitivity of the hypothalamic regulator decreases. (The quantity of hormonal receptors on the cell membrane is reduced if the concentration of the hormone related to these receptors increases in the blood. As a result, the organism is protected against an excess hormonal effect.)

In addition, as a result of changes in the cell (plasma) membranes, in particular, owing to the accumulation of cholesterol therein, the ability of the receptors to translocate decreases, thereby reducing the perception of hormonal signals. The concentration of neuromediators also decreases. It is precisely these phenomena that are observed in normal aging.

Thus, interdependence of both laws leads to a consequence of decisive significance in the life of each individual.

The law of deviation of homeostasis is not abrogated when the organism's developmental program is carried out to completion. On the contrary, it continues to be realized with the same consistency as earlier. Therefore, if deviation of homeostasis at first serves the purposes of development and growth, it later transforms into a force disturbing the constancy of the internal environment. As a result, features characteristic of normal aging and diseases of aging gradually develop. This is the reason why disturbances in regulation lie at the basis of natural death in higher organisms. The processes occurring quite acutely in the Pacific salmon occur much more slowly in mammals. Only the forms of the phenomena, not the phenomena per se, change.

The data in Table 1 demonstrate that the causes of death in such mutually remote species, as, for instance, Pacific salmon, rat, and human being, practically coincide. If the discussion did not concern the mechanism of death, it would be possible to say that this mechanism is a miracle of perfection.

Hence, aging in higher organisms, including humans, is directly associated with development, i.e., the same factors that ensure the organism's development conti-

Table 1. Comparison of Regulatory Causes of Death in Pacific Salmon, Rat, and Human Being

Pacific salmon (by B. Weksler, 1976)	Rat	Human being
Increase in blood sugar concentration	Increase in blood sugar concentration	Increase in blood sugar concentration
Increase in blood free fatty acid concentration	Increase in blood free fatty acid concentration	Increase in concentration of insulin in blood
Increase in activity of adrenal cortex	Increase in concentration of *triglycerides* and cholesterol in blood	Increase in concentration of *triglycerides* and cholesterol in blood
Atrophy of thymus	Increase in activity of adrenal cortex	Increase in activity of adrenal cortex (relative surplus of cortisol)
Obesity	Obesity	Obesity
Increase in concentration of cholesterol in blood (up to 1000 mg % when spawning)	Atrophy of thymus with decrease in immunity	Decrease in cellular immunity

Table 1 (concluded)

Pacific salmon (by B. Weksler, 1976)	Rat	Human being
Death due to infarction of myocardium, brain, kidneys and lung	Death due to arteriosclerosis, tumour of pituitary gland, infections, and cancer	Death in 85 out of 100 (on the average) middle-aged and elderly adults due to: obesity, diabetes mellitus in obese humans, hyperadaptosis, climacteric, atherosclerosis, metabolic immunodepression, autoimmune diseases, hypertension, mental depression, and cancer — the major (noninfectious) diseases

nue to be active after growth and sexual maturation are completed, being at the same time the cause of aging. The signs of aging are extremely uniform in all the individuals of every species, including humans, because development occurs according to a strict genetic program.

Nevertheless, this does not mean that aging is programmed. We are speaking here of the transformation of the developmental program into a mechanism of aging and age-related diseases. Therefore, only eight to ten diseases of the many hundred known are the cause of death in 85 out of every 100 middle-aged and elderly humans under natural conditions.

However, the fact that these diseases develop without fail, as if by a certain plan outlined by developmental mechanism, is a source of optimism. Indeed, if aging and age-related diseases developed because of numerously diverse and accidental causes, the search for a way to counteract their development would be severely hampered. And what is more, the dependence of certain diseases on the strict order of the internal factors of an organism's development and on many external factors, whose chaotic occurrence seems to refute the idea of order established by the law of deviation of homeostasis, has made it impossible for many years to see all that which is similar in the disturbance in homeostasis and which conditions the origin of these diseases.

The concept of deviation of homeostasis assists in finding some order in this chaos of vital events and in creating a new system of influences on the major human diseases. Special attention should be focussed, in particular, on the following circumstance.

An increase in the capacity of the principal homeostats in the aging process means that aging and age-related diseases do not occur because of a decrease or fading away of the activity of systems regulating the energy processes, adaptation and reproduction, but, on the contrary, due to their intensification and excess tension. This very important point seems quite improbable because we all know that the organism's capacity for work, strength, reproductive potency, and endurance decrease with age. But all of this is a result of aging and we are discussing here how aging begins. During aging, life seems to be uncontrolled (as happens sooner or later in a thermostat if its regulator can no longer control the temperature rise in the system because of its decrease in sensitivity).*

For example, it is known that the heart weakens in the course of time. But this is

* The idea of incompatibility of stability and development is discussed in several works: to begin with, in the works by E. Bauer (1935); in A. Comfort's (1979) figurative expression on the "homeostasis drift", or in the use of the term "homeorrhesis" suggested by Waddington (1957) for the determination of genetic concepts. But, no conclusions on how deviation of homeostasis occurs in the process of aging and on how the unity of the developmental mechanism, aging and age-related diseases is maintained at the regulatory level (or principle) follow from these works and statements.

preceded by an increase in its size, i.e., an increase in its capacity. An aging human functions as if ascending a staircase. But if this is true, then the search for ways and means of influence essentially change. In the light of new concepts it is often necessary not to stimulate, but on the contrary to inhibit, the activity of one or the other system.

Based on the law of deviation of homeostasis it becomes clearer why everything happens in exactly this way and not otherwise. And what is more, the law of constancy of the internal environment restricts the sphere of application of the law of deviation of homeostasis to three basic homeostatic systems. In other words, all the physiological parameters of the organism that are protected by the law of constancy of the internal environment do not participate in the development of the regular age-related diseases.

In addition, all this indicates that the major diseases of higher organisms cannot be eliminated without interfering with these biological regularities, because these diseases represent the high, but quite acceptable, cost for the perfection gained during evolution. Homo sapiens, who is not only the highest product of living Nature, but also its tool, which now at this new stage accelerates, changes and improves the evolution of living nature, and, consequently

itself, must interfere with this dialectically contradictory influence of the laws of stability and of deviation of homeostasis.

Therefore, in the next three chapters let us discuss how the age-related changes in the activity of the three basic homeostatic systems, induce the onset of three normal diseases, viz., hyperadaptosis, climacteric, and obesity, which always develop at a varying rate as a result of regular deviation of homeostasis in the process of ontogenesis.

Chapter 4

Hyperadaptosis: a Normal Disease of the Adaptational Homeostat

> An aging human begins to live as if in a state of chronic stress, and therefore becomes increasingly less protected when real stress lays its claims on the organism. Time is a universal stress factor.

In the previous chapter we discussed how homeostasis is disturbed under the influence of unfavourable external stress factors and, as a result, certain diseases develop if the stressful condition is too intense, or continues for too long. At the same time, protection against the effect of stress factors, or, as this phenomenon is commonly called, adaptation to changes in the external and internal environments is one of the main properties of a living organism. Unicells and complex higher organisms possess the capacity for adaptation, though, naturally, it is manifested differently.

The structure of unicells does not ensure reliable protection when there are significant changes in the external environment. Correspondingly, the major form of adaptation in unicells is variability, i.e., the loss of its initial individuality. The adaptation of microorganisms to toxic substances, in particular, antibiotics, is based on this property.

Higher organisms, on the contrary, preserve their individuality by means of specific protective mechanisms, which is consistent with the principle of maintaining the homeostasis. These mechanisms accomplish the variations that are necessary for protection but, at the same time, they preserve the ability of the organism to return to the initial state when protection is no longer required.

Adaptation to damaging factors is accomplished at all the levels of the organism, beginning with the cellular level. However, there is a specialized adaptational system, or adaptational homeostat that realizes the homeostatic protective reaction in higher organisms. The basic components of this system are the adrenal cortex, which produces cortisol, the hormone of protection; the pituitary gland, which produces corticotropin to regulate the release of cortisol; and, finally, the hypothalamus, which controls the secretion of corticotropin (Fig. 4). These three elements follow the commands of the feedback mechanism. For example, if the concentration of cortisol in the blood increases, then in accordance with the feedback mechanism it inhibits the activity of the hypothalamo-pituitary complex, and correspondingly, the production of its regulator, corticotropin. As a result, the secretion of cortisol by the adrenal cortex decreases.

The presence of this interdependence is easily verified as follows. An animal is administered a certain amount of cortisol,

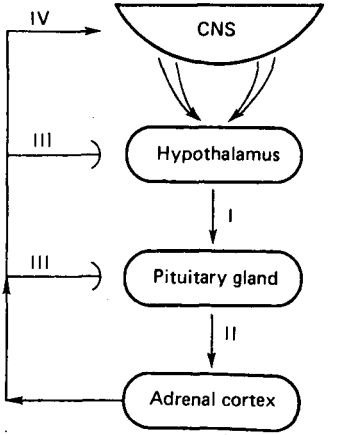

Fig. 4. Structure of the adaptational homeostat: I—hypothalamic hormone that stimulates production of corticotropin; II—corticotropin, hypophyseal hormone that stimulates production of cortisol by adrenal cortex; III—cortisol, adrenal cortex hormone that acts on the hypothalamus and pituitary gland through negative feedback; IV—cortisol exerts its effects at the level of the central nervous system (CNS)..

or dexamethasone, its derivative. Dexamethasone, which inhibits the secretion of corticotropin by negative feedback decreases the activity of the adrenal cortex, which

is controlled by corticotropin, i.e., decreases the secretion of cortisol.

If the same dose of dexamethasone is used, then the concentration of cortisol in the blood depends on the sensitivity threshold of the hypothalamus to dexamethasone. For example, the level of cortisol in the blood decreases by 51% in two-month-old rats under the effect of dexamethasone, and only by 11% in eight-month-old rats. Consequently, dexamethasone test demonstrates a decreased inhibiting effect on the hypothalamus in the older animals. In other words, the sensitivity threshold of the hypothalamus to the inhibiting effect of the working hormone, dexamethasone, increases with age. This simple experiment is surprising in its informativeness: it simultaneously demonstrates the mechanism and the fundamental law of biology, i.e., the law of constancy of the internal environment, and its antipode, the law of deviation of homeostasis.

The same phenomenon is observed in humans. For example, a given dose of dexamethasone decreased the concentration of cortisol in the blood by 33% in a group of humans whose average age was 50.5 years, and by 47% in younger people (average age 35.4 years). This means that with age the hypothalamus is less able to perceive regulating signals, becomes less sensitive to these signals, and this inevitably results

in a disturbance of the law of constancy of the internal environment.

Disturbance of this fundamental law leads to the development of a disease because a stable environment is the main condition for preserving the "quality of life" and the individual's life per se. During aging the adaptational homeostat continuously experiences effects that arise acutely during periods of stress when the organization of protection against the damaging agent (stress factor) demands an increase in the working capacity of the organism. The supply of energy, viz., glucose and fatty acids, as well as an increase in the concentration of the protective hormone, cortisol, is of fundamental significance in the organization of antistress protection (Chapter 2).

But according to the mechanism of negative feedback, an increase in the concentration of cortisol in the blood should induce a decrease in its production. However, if the hypothalamic sensitivity threshold to inhibiting signals increases, then the mechanism of negative feedback operates with a time lag, or is insufficiently effective in general. Therefore, the adaptational hormones exert an excessive, i.e., an undesirable, influence on the organism in the course of normal aging as a result of a disturbance in regulation.

Thus, if you carefully look at a man who is approximately 45 to 50 years old and is

still strong, you will see that his legs are thinner than they should be to correspond to his trunk, and the features of his face are more rounded than in young men, who are, possibly, not so strong physically. These variations are indications of the effect of excessive cortisol on the organism.

In essence, the age-related increase in the hypothalamic threshold in the adaptational homeostat creates a normal, i.e., a regular, disease that can be called "hyperadaptosis". Indeed, hyperadaptosis is a disease because the excessive reaction to stress induces a decrease in the vital capacity of the organism. But hyperadaptosis is a "normal disease" because it always arises during aging of the organism and not under the influence of external causes or accidental breakdown of the regulator.

What is the difference between hyperadaptosis and adaptation diseases?

It is known that the adaptational homeostat that assists the organism in enduring the onset of harmful effects of the external environment is itself subjected to changes under the influence of stress factors. Adaptation diseases, i.e., diseases that develop in the process of effecting protection, are associated with these changes. Hyperadaptosis develops because of internal reasons that change the system of regulation in the adaptational homeostat irrespective of the influence of external stress agents.

It is precisely the hypothalamic shifts, which are typical of normal aging, that result in the less effective regulation of the adaptational system and in its increased inertness. The hypothalamic regulator not only loses its ability to respond "keenly" to the changes in the external and internal environments, but, in part, it begins to live a kind of detached life, gradually creating disturbances in the adaptational system itself. In a certain sense it is better not to depend on the main regulator than to have a poorly operating one.

Therefore, hyperadaptosis also arises under the most favourable circumstances, just under the influence of the time factor. But hyperadaptosis is not only a "normal disease of aging", which introduces features of chronic stress into the life of the organism. When a real stressful situation arises, the unregulated adaptational system does not establish equilibrium for a longer time than normally, and its response to stress becomes excessive on the whole.

The latter case is clearly illustrated by data on the stress reaction caused by surgery (Table 2). Pre-operative patients with a decrease in the sensitivity of the hypothalamo-pituitary system in the dexamethasone test (group II) showed a higher increase in the concentration of cortisol in the blood than the patients with normal sensitivity to dexamethasone (group I). In addi-

Table 2. Blood Concentration of 11-Hydroxycorticosteroids (nmol/l) Depending on Sensitivity to Dexamethasone in Patients with Carcinoma of Stomach During Surgical Operation

Time of blood sampling	I – dexamethasone-sensitive patients	II –dexamethasone-resistant patients
Prior to operation	395±36.7	450±35.6
End of operation	775±72.3	903±1.7
After operation:		
1 day	428±45.5	508±64.3
9 days	400±46.1	527±42.5

tion, it was precisely the excessive antistress reaction that combined with a greater number of various complications after surgery (13% and 39%, respectively).

But as aging progresses, regulatory disturbances arise in the adaptational system in an increasing number of people. Therefore, the organism pays more for its protection in old age than during its youth. Aging per se forces a person to live as if in a state of constant stress even when no such stress exists. The storm of metabolic shifts arising during aging is at first not so extreme as in the case of stress, but the storm does not abate and it gradually destroys the foundation of health, the constancy of the internal environment.

Hyperadaptosis is one of the reasons why an elderly person can exist within a narrow-

er range of changes in the internal and external environments. Quite frequently minor factors, such as worry, physical overstrain, digestive disturbances, or even a light cold, may be the cause of sudden, seemingly unfounded death—death due to old age, as it is frequently referred to.

However, though the latter statement is generally recognized even in gerontology, it is vulnerable in many aspects. First and foremost, a decrease in the capacity for adaptation (as evidenced by death due to insignificant factors) is, in essence, also a consequence of a disease, hyperadaptosis, and of the accumulation of damages in various organs and systems that accompany hyperadaptosis and similar age-related processes. Meanwhile, the direct cause of hyperadaptosis is the decrease in the concentration of neuromediators in the hypothalamus, primarily, dopamine and serotonin. In this respect, hyperadaptosis is similar to mental depression. This is the reason why prolonged stress situations frequently worsen one's mood, while in old age mental depression to one or another degree is a common, i.e. a normal, phenomenon.

Nobody dies of old age. A human dies in old age of diseases, though in some cases this is not self-evident. Hyperadaptosis is an unusual disease: it develops in everyone, is not caused by obvious reasons and, therefore, seems non-existent.

A living organism pays for its adaptation to external influences by accelerated aging. Then disturbance of adaptation, which arises in the process of normal aging, pays this fare without any call for protection, in essence, in spite of the organism. That which caused adaptation, in the final end, deprives the organism of the ability to adapt to the most moderate requirements set by life, and owing to the effect of internal factors induces a disease, viz., hyperadaptosis.

But what are these factors that so significantly alter the reactions of the organism? It can be stated most generally that they are the forces that served the development of the organism. It will be seen in the following chapter that this is precisely so.

Chapter 5

The Climacteric: Normal Disease of the Reproductive System

> The climacteric is the norm and, at the same time, it is a disease. It is the norm because it is a regular phenomenon in the female organism, and it is a disease because it indicates a stable disturbance of regulation, causing, in the final end, a decrease in the vital activity of the organism.

As in all systems controlled by the hypothalamus, three structural storeys can be distinguished in the reproductive system: the hypothalamus, the pituitary gland, and sexual glands.

The hypothalamic sexual centre produces a gonadotropin releasing hormone (GnRH) which stimulates the secretion of gonadotropic hormones by the pituitary gland, which are regulators of the sexual glands. In their turn, the gonadotropins stimulate the production of sex hormones by the sexual glands and maturation of the sex cells. This three-component system is controlled by the negative feedback mechanism. In particular, the female sex hormones possess the capacity to inhibit the activity of the hypothalamus, thereby reducing the release of gonadotropins.

The reader certainly understands by now that if this mechanism always operated ac-

cording to the rules of classical cybernetics, it would have preserved the stability of the system, but it would be this stability that would prevent development (just as a temperature rise above the norm is prevented by a thermostat in good repair). But it is well-known that there is no such stability in the reproductive system. All higher animals are born sexually immature and sexual maturity occurs in due time.

How is sexual maturation inhibited until the time the organism is ready for reproduction?

To answer this let's examine a model of the sexual maturation mechanism suggested already in 1959 by two researchers, B. Donovan and J. J. Van der Werff Ten Bosch.

The hypothalamus in mammals, including humans, is characterized immediately after birth by high sensitivity to the inhibiting influence of the sex hormones that are already produced by the sexually immature organism. Therefore, the activity of the sexual centre of the hypothalamus is suppressed through negative feedback between the stated centre—the hypothalamus—and the working organ—the sexual glands. Under these conditions the hypothalamus does not stimulate the production of pituitary hormones that control the activity of the sexual glands, and the entire reproductive system is in a state close to calmness. This

equilibrium would be preserved for a long time, theoretically, in the course of the entire lifetime, if the sensitivity of the hypothalamus to the sex hormones remained at the same level. But the sensitivity of the hypothalamus to the inhibiting influence of the sex hormones decreases with age. This phenomenon can be illustrated by the following experimental data.

To suppress the activity of the hypothalamus by 50% in one-month-old rats (i.e., before maturity), 0.5 μg of diethylstilbestrol, an analogue of the female sex hormone, must be injected each week. Four times more of this preparation is necessary to suppress the sexual centre of the hypothalamus in a mature animal. But if the sensitivity threshold of the sexual centre to suppression rises, then the hypothalamus is gradually freed of this inhibitor, and thereby increases its activity and, finally, stimulates the development of the sexual glands. In accordance, the production of sex hormones also increases, which induces the development of secondary sexual characteristics, and so on. Hence, sexual maturation is based on the increased activity of the hypothalamus, or, to be more exact, on the increase in the hypothalamic sensitivity threshold to the sex hormones.

Let's try to understand why the rise in the hypothalamic threshold is of key significance in sexual development. Sexual mat-

uration is inseparable from an increase in the capacity of the reproductive homeostatic system. But bearing in mind that any homeostatic system consists of a regulator and a working organ, and that their interaction is conditioned by the feedback mechanism, it is easy to understand that a rise in the sensitivity threshold of the regulator (in the given case, the hypothalamus) is the only way of increasing the capacity of the system, and, at the same time, preserving the feedback mechanism.

Let's assume that an increase in the system's capacity occurs by another way, viz., by the independent increase in the activity of the working organ, the sexual glands. In this case an increase in the sex hormone concentration in the blood because of negative feedback between the working gland and its regulator would firmly inhibit the activity of the regulator, the hypothalamus: it would eliminate the very possibility of regulation and development. This situation is observed, for instance, when a tumour that secretes hormones develops in the sexual glands. A tumour that produces an excess quantity of sex hormones causes the appearance of secondary signs of maturation, but it is unable to induce true sexual maturation. In this case, the capacity for fertilization is lacking owing to stable suppression of the hypothalamic regulator by the high level

of sex hormones which exert their effects through negative feedback. Hence, the assumption is wrong that the increase in the activity of the peripheral element in the homeostatic system is the key factor in the maturation of the reproductive system.

But with an increase in the system's capacity, when a rise in the sensitivity threshold of the hypothalamic regulator to the sex hormones is the key mechanism, these hormones are unable to firmly inhibit the activity of this mechanism. On the contrary, this activity is gradually intensified and the hormones that stimulate the sexual glands—the gonadotropins—are secreted in increasing quantities, forcing the sex glands to function more and more intensively until sexual maturation is complete.

The data in Table 3 demonstrate the type of changes that are unusual in the cybernetic (reproductive) system during which the concentrations of the central regulating hormones—the gonadotropins—and the peripheral female sex hormone—estradiol—increase in the blood simultaneously. At the same time, the capacity of the reproductive system for cyclic functioning is preserved due to the active state of the hypothalamic regulator, which is gradually freed from the inhibiting influence of the sex hormones.

This was roughly the first model for the mechanism of sexual maturation. Later,

Table 3. Age Dynamics of Gonadotropins and Estradiol in the Blood of Girls (Janner et al., 1972)

Age period	Gonadotropins		Estradiol μg%
	FSH (μg%)	LH (μg%)	
P_1	0.73±0.3	0.8±0.1	7±1
P_2	1.78±0.5	1.12±0.2	13±2.4
P_3	2.25±0.5	1.08±0.2	25±4.5
P_4	2.62±0.4	1.68±0.2	44±12
P_5	2.53±0.4	2.4±0.6	58±57

Note: P_1-P_5 designate different periods of maturation of the organism that end in period P_5 with switching on of the reproductive function.

it became necessary to introduce some changes, proceeding from additional data on the function of the sexual centre (V.M. Dilman, *Endocrinological Oncology*, 1974). The new version took into account the fact that the hypothalamic sexual centre in the female has both tonic and cyclic regions. The data given above relate precisely to the changes occurring in the tonic centre during development. These changes ensure sexual maturation in both the male and the female.

However, to switch on the reproductive cycle in the female organism, not only sexual maturation but also special stimulation of the cyclic centre are necessary. This stimulation is effected by the female

sex hormones as follows. The shifts in the system, which are controlled by the tonic centre, induce an increase in the production of female sex hormones. When their concentration reaches a certain level, the female hormones stimulate the cyclic centre to induce ovulation by the mechanism of positive feedback, i.e., the release of ovum from the ovary. As a result, the required conditions for fertilization are created. The female reproductive system begins to function in cycles, ensuring this ability for many years.

The latter model, however, describes only the period of sexual maturation. Some time earlier (1958-1971) the author postulated a *hypothalamic model of the age-related switching off of the reproductive function**. It thus became possible to combine both these processes by assuming that the age-related switching off of the reproductive function is accomplished by the same mechanism that ensures its age-related switching on and sexual maturation.

Indeed, the concept that the age-related switching off of the reproductive capacity in the female is a phenomenon connected either with the exhaustion of the store of follicles in the ovaries, or with a decrease in the sensitivity of the ovaries to their

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* V. M. Dilman, *Endocrinological Oncology*, Meditsina, Leningrad, 1974; 1983 (in Russian).

regulators, the gonadotropins, is still dominant today. The author's explanation for the switching off of the reproductive system is that this process, on the contrary, is conditioned by an increase in hypothalamic activity, i.e., by regulatory shifts. Let us attempt to examine this, proceeding from the assumption that the rise in the hypothalamic threshold of sensitivity up to sexual maturation occurs in the tonic centre and later also begins in the cyclic centre.

The rise in the sensitivity threshold in the cyclic centre requires an increase in the concentration of female sex hormones in the blood, otherwise their concentration would be insignificant to induce ovulation when acting on the cyclic centre. (The latter assumption as pertaining to the action of estrogens on the cyclic centre was confirmed later in several works, V.N. Babichev, 1981; K. Lu et al., 1977.)

In turn, the increased production of sex hormones is ensured with the increase in age by the continuing changes in the tonic centre that were so necessary earlier for sexual maturation.

This can be judged indirectly on the basis of data on the age-related increase in the secretion of the pituitary gonadotropins that control the activity of their target gland, the ovaries. Thus, the secretion of the sum total of gonadotropins in women

between 25 and 35 years of age increases threefold. Meanwhile, the system of reproduction is already fully switched on by the age of 25, and the concentration of the regulator hormones reaches its optimal value. Hence, the threefold increase in this level is not governed by the requirements of development and sexual maturation.

In other words, the reproductive system still continues to increase its capacity after reaching maturity*. However, it is theoretically apparent that the rise in the hypothalamic threshold in the cyclic centre, which continues in the process of aging, nevertheless at some age causes a disturbance in the functioning of the system, thereby switching off of the reproductive function. This occurs when the concentration of the female sex hormones in the blood drops below the critical level for inducing ovulation. Thus, the age of the climacteric is determined, on the one hand, by the rate of increase in the hypothalamic threshold in the cyclic centre during aging, and, on the other hand, by the degree compensation by the ovaries, i.e., by their capacity to increase the production of female sex hormones

* In this discussion, the problem is treated schematically. Direct studies showing an age-related rise in the sensitivity threshold of the tonic centre are found in: V. M. Dilman, *Endocrinological Oncology*, Meditsina, Leningrad, 1983 (In Russian).

under the influence of the age-related rise in the gonadotropin concentration in the blood.

Therefore, the greater the compensation, i.e., the increased production of female hormones by the ovaries, which could overcome the trend to switch off the mechanism of self-regulation in the reproductive homeostat, the later the induction of the climacteric and menopause. Consequently, the rise in the concentration of sex hormones is a compensating process, which is created by a rise in the hypothalamic sensitivity threshold in the tonic centre, but is directed toward overcoming the age-related rise in the hypothalamic threshold in the cyclic centre.

In summary, it can be concluded that the rise in the hypothalamic threshold in the reproductive homeostat first ensures the age-related switching on and then the age-related switching off of the reproductive function.

The regulatory nature of the latter phenomenon is confirmed by the following sophisticated experiment. Japanese scientists (Kushima et al., 1961) spayed female rats belonging to two age groups, young and old. Then the ovaries of the young animals were transplanted into the old animals. If the age-related switching off of the activity of the ovaries depended on the age of their own ovaries, the operation would in-

duce recovery of their activity. However, the young ovaries failed to function in the old animals. But when the ovaries of old rats were transplanted into young animals, their ovaries began to function.

In other words, the hypothalamus imposes its rate of aging on the ovaries. Indeed, calculations indicate that about 2500 follicles, containing ova, are expended during the entire reproductive period in women. At the same time, both ovaries contain the germs of about 500 000 follicles, i.e., 200 times more than are used during the lifetime. It goes without saying that the reproductive function differs somewhat between human beings and animals; however, the principle of the age-related rise in the hypothalamic sensitivity threshold to the sex hormones remains invariable.

True, it was unclear for some time whether the changes occurring with age were reversible at the hypothalamic level. Was there a way to influence the mechanism of regulation such that the activity of the ovaries could be recovered?

Recent experiments on animals suggest a positive answer to these questions. Thus, the cyclic activity of ovaries in animals was recovered in our laboratory by means of epithalamine, a hormone produced from the pineal body, an endocrine gland.

A similar experiment with analogous results was carried out by Prof. Joseph Mei-

tes and co-workers (USA). He used another preparation, levodopa (a precursor of dopamine), which has a similar effect on the hypothalamus. Thus, the experiments demonstrated the possibility of influencing one of the most typical manifestations of aging, viz., the cessation of the capacity for reproduction.

The model for the age-related switching on and off of the reproductive function also assists in understanding how in general normal development is transformed into aging and diseases of aging.

As the reader will recall, when the hypothalamic mechanism switches on the reproductive function, it continues to function, ensuring for a certain period the preservation of the reproductive function.

But, take note! It turns out that an age-related increase in the secretion of regulator-hormones (gonadotropins) and hormones secreted by the ovaries (estrogens), which in essence reflects a disturbance in the constancy of the internal environment, is "useful" because precisely these shifts ensure preservation of the capacity for childbearing, and counteract the switching off of the reproductive function for a certain period of time. However, it is not without reason that the word "useful" is given here in quote marks. All that described above can be considered neither advantageous, nor disadvantageous, though

both estimations are simultaneously applicable to the events discussed. It would be more correct to say that it is "so arranged by nature" because the factors that first ensure sexual maturation later ensure preservation of the reproductive function over the course of many years. The same mechanism, however, determines the age-related cessation of the capacity for reproduction in the female.

At the same time, many researchers insist that the age-related switching off of the reproductive function is advantageous because it solves at once several problems: a) it limits the number of organisms in the population, which contributes to the maintenance of an optimum quantity of individuals in the given living space; b) it reduces the probability of congenital defects whose frequency increases in the progeny with the age of the maternal organism; and c) it regulates the rate of natural succession of generations under the conditions of a wide exchange of hereditary material as opposed to what it would be in the absence of age-related limits of reproduction.

The mechanism of age-related switching off of the reproductive function is truly in conformity with the realization of all these requirements. In other words, this mechanism is biologically expedient because it contributes to increasing the vitality of the species. But in reality, all these cat-

egories of usefulness are not realized purposefully, i.e., they are not accomplished for the well-being of the species as "predetermined by nature", but exist simply because the age-related switching on and off of the reproductive function in higher organisms is realized by one and the same hypothalamic process. All the rest represent only consequences of this process that are not associated with the biological idea of meeting the requirements of the species, although they satisfy these requirements by the most rational way (see Chapter 11).

It immediately becomes clear that the idea of usefulness is conditional when attempting to apply this evaluation to concrete changes in each individual in the process of aging. The production of gonadotropins increases with age. On the one hand, this increase is necessary as it is a part of the mechanism that switches on the reproductive cycle during development. But this phenomenon represents a disturbance of the law of constancy of the internal environment in the organism. As regulator-hormones, gonadotropins, compel the sexual glands to function more intensively. If the quantity of gonadotropins in the blood increases almost tenfold by the time of the climacteric and menopause, it means that the ovaries are undergoing intensive stimulation resulting in an increase in the production of sex hormones. This increase

is necessary, certainly, to preserve the feedback mechanism in the reproductive homeostat under conditions of a continuously rising hypothalamic threshold. At the same time sex hormones render an excessive stimulating effect on the organs of the reproductive system.*

Excessive stimulation of these organs frequently induces metrorrhagia during the climacteric period. A quite peculiar situation arises: the greater the quantity of sex hormones produced, or rather, the more the compensation is expressed, the longer the reproductive function is preserved, creating an impression of well-being and health. But in this case associated changes induced by the excessive influence of the sex hormones on the organs of the reproductive system are more likely to be expressed. In other words, the longer the reproductive period in a woman, the greater is the probability of diseases associated with the mechanism of compensation. In this sense, the onset of metrorrhagia, which is a disease, is a by-product of the organism's "effort" to counteract the onset of the climacteric.

At the same time, it has been statisti-

* However, the stimulating effect of the hormones decreases due to the phenomenon of desensitization, i.e., a decrease in the concentration of the receptors of these hormones induced by the increase in their concentration in the blood.

cally noted that frequently the reproductive function has been switched off later than usual in women who fall ill with breast cancer after menopause. Indeed, menopause commences later when the process of compensation is more clearly expressed (see above). But increased compensation, which is realized by the sex hormones, contributes to the development of climacteric bleeding and even tumours of the reproductive system because of its stimulating effect on the organs of the reproductive system.

The role of increased stimulation of an organ in the development of cancer has been demonstrated in many experiments on animals. Thus, if a rat is spayed, the production of gonadotropins in the animal increases to its maximum because the inhibition that is usually realized by the sex hormones through a negative feedback mechanism has been eliminated. Then, if the removed ovary is transplanted into the spleen and the experiment continues for a long time, the gonadotropins, which act on the transplanted ovary, induce the development of ovarian tumours. This demonstrates the development of a tumour owing to a disturbance in the law of constancy of the internal environment (in the given case the disturbance is an increase in the gonadotropin concentration in the blood; see Chapter 10).

It cannot be ruled out that the age-related increase in the incidence of ovarian carcinoma in humans is associated with an increase in the production of gonadotropins*. In this case nature accurately reproduces the mechanism of the experiment described above without knowing whether the shifts in the internal environment that arise during aging are dangerous for the individual.

Thus, the same process of compensation, which is an inseparable part of development, with time induces pathologic changes, or a disease. On the basis of the mechanism of their onset, it is logical to call these diseases, which are associated with the process of development, as diseases of compensation. The mechanism of the age-related cessation of the reproductive function—the climacteric—being a physiological process, is from this point of view also a disease of compensation, or a normal disease: it is a disease whose pattern of onset is conditioned by the natural mechanism of the organism's development.

* Statistical data in favour of this assumption indicate that long-term use of contraceptive steroid preparations, which suppress the production of gonadotropins, decreases the incidence of ovarian carcinoma. The mechanism of this advantageous effect can also be associated with decreased traumatization of the integumentary epithelium of the ovaries, which occurs with rupture of a follicle when ovulation is not suppressed.

In this example of the transformation of the mechanism of development into the mechanism of aging and diseases of aging one can easily perceive a manifestation of the dialectical principle of transition from quantity to quality. In particular, a rise in the gonadotropin concentration at the beginning is part of the mechanism of the age-related switching on of the reproductive function. Later, it characterizes an opposite process, i.e., the age-related switching off of the reproductive function in the course of a subsequent increase in their concentration in the blood.

The cause of these diseases is incorporated in the developmental mechanism per se, i.e., in the genetic program, whose realization is directed toward the age-related increase in gonadotropin production. Thus, another law of dialectics is manifested, viz., the unity of opposites that lies in the essence of the phenomena. The motive force, which by means of gonadotropins ensures two interrelated processes that are opposite in physiological significance, reveals the concealed principle of the law of the unity of opposites. This is a unity that includes the mechanism of development and the negation of development by its transformation into a many-sided phenomenon of aging and age-related diseases.

In the given case this is all realized on account of the law of constancy of the inter-

nal environment and the law of deviation of homeostasis. Indeed, preservation of the reproductive function over a long period of time (which corresponds to the effect of the law of constancy of the internal environment) is ensured by a compensatory increase in the production of sex hormones, i.e., it is gained on account of an opposite law, viz., the law of deviation of homeostasis. This is really a unity of opposites, in which the latter are so carefully veiled that their external manifestation seems most advantageous. The longer the period of reproduction, the more remote aging, which is always intuitively associated with cessation of the capacity for childbearing, appears to be.

But the fact is that although acting in unity, the opposites do not lose their essence: prolongation of the childbearing period simultaneously creates conditions for the earlier cessation of life owing to the increasing probability of cancer of the reproductive system. The relationship of the climacteric with climacteric bleeding and with the increasing incidence of tumours in the reproductive organs illustrates quite vividly the two-faced image of the climacteric. The two faces of the climacteric—the norms and the diseases—characterize the absence of a border between age and disease, and between norm and pathology, revealing once again the essence of unity

of opposites, which are concealed in every natural phenomenon.

If we ponder it over, we see that in the given case we have a model of transformation of the mechanism of development into a mechanism of aging with its regulatory type of death, although the contribution of the reproductive homeostat to the concrete causes of death in mammals is apparently not so great.

The contribution introduced by the reproductive homeostat in the example relating to the death of Pacific salmon is beyond all question more significant. In this case, however, the changes in the reproductive system involve other systems, primarily the energy and adaptational one, which in a triple alliance "administer unlawfulness" within the framework of the law of deviation of homeostasis.

It is precisely the energy shifts that in the final analysis determine the character of aging pathology. This will be demonstrated in the following chapters that cover the energy system of an organism. The main problems in aging pathology will be considered using a model of obesity, because, figuratively speaking, higher organisms burn away in the flame of fats during aging.

Chapter 6

Age-Related Changes in Appetite Regulation

> A human being, who all his life is guided by his appetite to fulfill his food requirements, is inevitably "led astray".

Living organisms are open systems because they receive energy and matter from the environment and then return them. A living system is most stable in a stationary state when the intake of energy and matter is consistent with their expenditure. Therefore, to prolong the lifespan, it is theoretically necessary that the stationary state should be strictly maintained at one level after the cessation of growth in the organism.

However, this does not happen. The age-related increase in the fat mass of the organism is an obvious case. Why isn't the stationary state of the energy processes preserved?

An answer to this question is usually sought in the general laws of physics. But the law of increasing entropy is not decisive in open systems. One could theoretically imagine the existence of such a "living machine" wherein equilibrium is maintained permanently between the intake of matter and energy owing to the ability of the "living

machine" to regulate, renew itself, undergo repair, and adapt to the changing conditions of the internal and external environments. The fact that the stationary state is not preserved in a living system induces one to seek the reasons for instability not in physical but in biological laws.

The presence of a stationary state in an energy system would correspond to accurate realization of the law of constancy of the internal environment in the organism. At the same time, a natural disturbance in the stationary state occurs, as will be demonstrated, in conformity with the law of deviation of homeostasis. Though a living organism is primarily an "energy machine", which operates according to the laws of physics and chemistry, the machine cannot independently achieve stable maintenance of a stationary state because the loss of this state is dependent not on physical regularities, but on biological ones that the living system cannot rid itself of without losing the capacity for development, i.e., existence.

Therefore, it is possible to maintain that an organism, striving towards a stationary state at each given moment, never reaches it. In other words under normal conditions a stationary state exists at each given period of time, but it is lost over time, being subordinated to the dialectics of development.

Let us discuss some examples of the age-related obesity, and how the energy equilibrium in an organism is disturbed with increasing age. The age-related increase in the amount of fat is for brevity's sake called obesity, though it differs in certain respects from obesity, as a disease. It would be more correct to discriminate the disease obesity from the age-related obesity, since age-related obesity appears practically in everyone at one or another age while the disease obesity is the destiny of many but not all.

Even if the body mass does not increase with age, the content of fat increases while the mass remains stable because of the decrease in the quantity of muscular and bone tissues*. Considering that a 70-kg body mass of an adult man includes about 10 kg of fat, an increase in the body mass by 10-12 kg by the age of 50, as compared to the mass at 20, corresponds to a doubling in the amount of the adipose mass.

The significance of this change is seen by comparing the index of the increase in the adipose mass with any other index protected by the law of constancy. For example, a twofold rise in the arterial pressure is an indication of severe hypertension, and a twofold increase in the blood sugar is called diabetes mellitus.

* The term "body mass" is currently used instead of "body weight".

Why does the body fat mass increase with age? Usually this question is answered by the fact that an elderly person spends less energy than he or she receives. The surplus energy source leads to obesity.

However this answer is not quite reliable. It can be applied only in cases when the intake of food really increases, or the expenditure of energy decreases because of the reduced functional activity of the organism and correspondent heat production. Therefore, obesity can be easily reproduced in an experiment by overfeeding the subject. Likewise, by sharply reducing the functional activity and maintaining the usual norm of nutrition the body mass will increase.

At the same time, almost everyone can recall a period in their life (usually between the ages of 20 and 25 years) when, despite the variations in physical activity, ambient temperature and nutrition, their body mass remained practically stable. This means that regulation that is directed toward stabilization of the body mass exists.

The regulatory mechanism can limit the body mass by two ways: by controlling the quantity of energy taken in by the organism with the food, or by regulating the heat production and heat transfer. The first method, i.e., the control of food consumption, or regulation of the appetite has currently been more thoroughly studied.

It would seem that everything will be reliable: if control of the body mass exists, then the appetite should be called upon to precisely reflect the consumption of energy by the organism. And, correspondingly, if the physical activity reduces with age, the amount of consumed food that is regulated by the appetite should decrease.

However, it is difficult to imagine such a device in the living organism that would store in its memory data on the ingress of energy substances into the organism and data on the expenditure of energy for a certain period of time in the past, which is much more complicated. What is actually true in reality?

The hypothalamic regulator, which controls the body mass, consists of two devices. The first one regulates the fat content in the organism indirectly by influencing the level of insulin in the blood. Insulin is a hormone secreted by the pancreas, which is necessary for the assimilation of glucose by the cells. The concentration of insulin before feeding rather strictly corresponds with the mass of fat in the body. If the fat mass increases, the level of insulin increases, which influences the respective part of the hypothalamus. As a result, a series of reactions occurs that induce a decrease in the fat mass and, thereby, decrease the insulin concentration. This hypothalamic device can be conditionally called "the stra-

tegic centre of the appetite" because it helps to control prolonged processes for maintaining constancy of the body mass.

The second hypothalamic device controls the concentration of energy substances in the blood, primarily, glucose, and, possibly, fatty acids. This regulator seems to measure the necessary amount of fuel, i.e., nutritional energy sources, and not for the long terms, as the first regulator, but for each given moment of food intake. Therefore, the second device can be called "the tactical centre of the appetite". Let's see how this second hypothalamic regulator controls the consumption of food from the standpoint of classical medicine.

The majority of investigators consider that two interrelated centres in the hypothalamus are "in charge" of the appetite: the food centre and the centre of satiation. If food is not supplied to the organism, the content of glucose in the blood decreases, and the food centre arouses the appetite. The content of glucose and insulin in the blood increases as a result of food intake. After reaching a certain level of concentration, the glucose stimulates the centre of satiation, thereby inducing the sense of satiation. At the same time, signals are transmitted from the centre of satiation, which induce inhibition of the activity of the feeding centre. (The scheme of appetite regulation is slightly simplified here.)

However, though classical medicine has determined how the appetite is regulated, it gives no answer to the question of why the regulation of the appetite is disturbed in an aging man. The experimental data available indicate that the appetite is stimulated when the centre of satiation is destroyed. But there are no data that point to the fact that the centre of satiation is destroyed by the age of thirty. Nevertheless, by this time there is already an accumulation of fat in the body. It is impossible to think of atherosclerotic affection of the centre of satiation, because in old age, when atherosclerosis is most expressed, the appetite begins to diminish. And finally, it is quite apparent that the appetite can vary at any age depending on many conditions, e.g., in the case of worry or fear, or, on the contrary, in a favourable emotional situation.

What then is the reason for losing hypothalamic control of the appetite during aging? It is assumed that the sensitivity of the hypothalamic centre of the appetite to the effect of glucose decreases in the process of aging, or, in other words, the sensitivity threshold of the satiation centre to the stimulating effect of glucose rises.

Indeed, the same amount of sugar in the food induces, over the course of many years, a greater rise in the glucose level in the blood (Table 4). Owing to the fact that glucose, while activating the satiation cen-

tre, in the final end, suppresses the appetite, the greater the glucose content in the blood after a meal, the faster, it would seem, the appetite is inhibited. In other words, satiation in the course of aging should take place faster during a meal than in young age. However, the body mass increases with age. This makes it necessary to admit that the satiation centre, on the contrary, becomes less sensitive to a rise in the glucose level. This is the reason why a middle-aged man manages to consume more food than necessary before the hypothalamic regulator of the appetite operates. An excess of glucose accumulates in the blood which over the course of time is not assimilated as well by the muscular tissue. The surplus glucose turns into fat.

The strategic appetite centre should certainly prevent the development of obesity under these conditions. The accumulation of fat, conditioned by erroneous functioning of the appetite's tactical centre and the associated rise in the insulin level in the blood should influence the strategic centre and induce reorganization of the "food behaviour" so that the body mass would drop to its original level.

Apparently, this occurs in some cases. If the body mass of a young man increases through overeating, it is frequently possible to observe an automatic drop in the appetite and a recovery of the initial body mass.

It has also been found that in the course of aging the body mass increases intermittently rather than continuously, i.e., there are periods when the body mass increases and then remains stable for a certain period of time. This occurs as if the set point, or, to be more precise, the sensitivity threshold of the regulator in the strategic centre of the appetite changes.

Hence, it can be assumed that one and the same phenomenon is realized in the "tactical" and the "strategic" appetite centres: a rise of the sensitivity threshold to the regulating signals transmitted to maintain stability in the energy system of the organism.

There is one interesting peculiarity related to this case. Beginning with childhood, a person grows to trust his or her sense of appetite. During one's youth, this trust is justified: the satiation and the strategic centre of the appetite react subtly to changes in the concentration of glucose and insulin in the blood, ensuring the requirements of development and also a certain stability of the organism. But over the course of years, the centre of the appetite begins to lead us astray.

Currently, certain details regarding the hypothalamic mechanism for regulating the appetite have become clear. In experiments, an artificial decrease in the concentration of nerve signal transmitters—the neuromedia-

tors—elicits an increase in the appetite in animals and humans. But the drop in the concentration of neuromediators is regular over the course of aging and it should induce a greater appetite. (The outline of the events is somewhat simplified here without taking into consideration other appetite regulators.)

The following is one more point of interest. It is commonly believed that one starts to lose weight when suffering from adverse emotions. This is significantly associated with a decrease in the appetite and a decrease in the amount of consumed food. On the whole this observation conforms with reality and this reaction is most characteristic of people who are still young. But it also happens that the appetite increases in middle-aged people in response to prolonged adverse emotions, and sometimes the body mass increases as well. How can this be explained?

The concentration of certain neuromediators, primarily, dopamine and serotonin, decreases in the hypothalamus with the advance of age. The state of stress also induces a decrease in the level of these neuromediators in the hypothalamus. Regulation of behaviour associated with stress is controlled by the hypothalamic centres that also deal with the regulation of the appetite. An acute sense of hunger may arise when the sum total of the influences of age and stress

induce a considerable decrease in the content of neuromediators. An increase in one's appetite in response to worry is an index that something is wrong, or, to be more precise, an index of significant expression of age-related disturbances.

The dependence of the appetite on one's mood is only one side of mutual relations. On the other hand, the mood can depend on the intake of food. The following joke is quite popular though not very elegant: the way to a man's heart is through his stomach. This thesis is based on intuitive observation of true physiological processes. If a man consumes his portion of meat, then the concentration of amino acids in the blood increases. The amino acids, including tryptophan, are the building blocks of protein. Serotonin, a hypothalamic neuromediator, is synthesized from tryptophan in the brain. Serotonin controls the mood and an increase in its concentration is physiologically the basis for improving the mood. In turn, the centre of satiation is stimulated by serotonin.

But carbohydrates, as everyone knows, can also be a factor that improves the mood. The production of insulin increases under the influence of glucose, which all sweets are transformed into no matter how fancy they look. The same hormone, just as it activates the transport of glucose into cells, contributes to the supply of tryptophan to the

brain, i.e., it also increases the level of serotonin in the hypothalamus. The good nature of gourmands, described frequently in fiction, is not only an inborn trait of character, but is also one that is developed by tasty food. There would be no harm in all this for a gourmand if the surplus insulin did not induce obesity, and if in the course of years the disturbance in the regulation of the appetite did not elicit a belated reaction of satisfaction, i.e., a distorted assessment of what is really necessary for the organism.

Thus, the age-related increase in the body mass is a symptom of a disturbance in the appetite conditioned by a rise in the sensitivity threshold of the hypothalamic centres to the regulating influence of food and insulin.

Age-related obesity is just as regular from this point of view as the development of the climacteric. But, just like the climacteric, it is an index of the loss of self-regulation and stability, and, most important, a loss occurring in the principal system of the organism: the system of energy homeostasis. The most regrettable point is that it is not only the "weighing device" of the energy homeostat that begins to operate inaccurately with age; regulatory disturbances in the homeostat itself also occur, which aggravate the error in the food scales.

The energy of the organism is the basis for its existence, and at the same time, it is the force that once having escaped regulatory control is chiefly responsible for the onset of the major diseases in man. This is the reason why it is so important to understand the intricacies associated with the system of self-regulation of the energy flux. And this is what shall be discussed below.

Chapter 7

Obesity: A Normal Disease of the Energy Homeostat

> Though fats burn away in the flame of carbohydrates, the latter do not burn in the flame of fats.

It is commonly recognized that ancient man lived only on carbohydrates, and that omnivorousness, which led to the consumption of meat and animal fat, was the decisive step toward modern diseases. This statement is not quite correct. Neither ancient people, nor anthropoid apes, regardless of the existing opinion, ever fed exclusively on carbohydrates. They always consumed carbohydrates and animal fat as a source of energy. It is true that ancient man received energy from plant food, utilizing mainly glucose as well as another carbohydrate —fructose—as the energy source. But irrespective of the initial food, if there is a surplus of glucose in the blood, it is transformed in the adipose tissue into fat by means of the hormone insulin. This occurs in conformity with the same scheme according to which domestic poultry accumulates fat when it is fed grain.

If the vegetable oils in plants are chemically related to unsaturated fat, then semi-

solid saturated fat is formed in the human organism from glucose (we obtain the same fat from animals). When no food is taken in by the organism, e.g., at night, this fat serves as a source of energy.

There is an antagonism between the two sources of energy, i.e., the carbohydrates and animal fat, which the energy homeostat is called upon to maintain.

In this system, glucose and fatty acids serve both fuel and factors of regulation. The two other basic elements of the energy homeostat are the hormones: insulin and growth hormone. Insulin is necessary for the assimilation of glucose. The energy system is organized so that glucose stimulates the release of insulin into the blood from the pancreas, i.e., the glucose itself creates conditions conducive to its burning, or catabolism, in the tissues.

Growth hormone functions in the energy homeostat as a fat-mobilizing hormone. The supply of fatty acids, the second type of fuel, from the fat depots increases under the influence of growth hormone.

When food is taken in by the organism, there is no necessity for using the fat accumulated as a reserve in the body proper. During this time the utilization of reserve fat is limited or even ceases, which is ensured as follows.

An increase in the glucose concentration in the blood is conditioned by the intake of

food and influences the glucose receptors in the hypothalamus. The latter decreases the release of growth hormone from the pituitary gland. Since growth hormone is characterized by a powerful fat-mobilizing effect, a decrease in its concentration results in a decrease in the concentration of fatty acids in the blood.

At the same time, glucose stimulates the release of insulin from the pancreas. Insulin is necessary for the catabolism of glucose in the tissues; therefore, it is natural that it can inhibit the mobilization of fat from the fat depots. This combined influence, viz., decrease in the growth hormone concentration in the blood and increase in the insulin concentration, greatly decreases the release of fatty acids into the blood. Under these conditions glucose becomes the principal energy source that is utilized by the organism.

Thus, conditions are created after the intake of food for utilizing the food energy while the reserve fat is preserved. And what is more, the reserves of fat are even supplemented, i.e., if excessive glucose has accumulated in the blood (e.g., due to the decrease in its utilization by the muscles), under the influence of insulin this excess transforms into fat. (Although in humans a maximum of 10 g of fatty acids can be synthesized in the adipose tissue per day, the surplus insulin synthesizes an increased

amount of fat from the glucose in the liver, whence it is transported in very low-density lipoproteins to the fatty tissue. In addition, a large amount of glycerol can be synthesized from the glucose in the fatty tissue per se, which in combination with fatty acids of food origin induces the accumulation of fat in the organism.)

The type of energy supply changes radically when the organism is deprived of food, e.g., at night, when no food is taken in by the organism. The system of the energy homeostat functions very "reasonably" under these conditions: it utilizes fat as fuel, whose reserves in the fat depots are much higher than the reserves of glucose in the "animal starch" glycogen. The glucose is preserved for the nervous tissue, being the principal source of energy for the latter. It is even "taken into account" that the reserves of glucose in the organism are limited. When abstaining from food, the mechanism that produces glucose from amino acids (proteins), which is the basis of gluconeogenesis, functions more intensively.

All these changes in the energy system are realized as follows. When there is no intake of food by the organism, the concentration of glucose in the blood decreases. As a result, the concentration of insulin, whose production depends on the glucose concentration, decreases as well. In accordance with the energy homeostat, the

decrease in the glucose and insulin concentration in the blood eliminates inhibition of the hypothalamic centre that controls the secretion of growth hormone by the pituitary gland. Correspondingly, the growth hormone level in the blood increases and the mobilization of fatty acids from the fat depots is increased. As the content of insulin in the blood decreases during abstention from food, the inhibiting effect of insulin on fat mobilization is eliminated, which intensifies the fat-mobilizing effect of growth hormone. As a result, the level of free fatty acids in the blood increases. The fatty acids become the basic energy substrate, the basic fuel that is catabolized by the organism.

Unlike glucose, which requires insulin for its transport into the cell through the cell membrane, the uptake of fatty acids by the muscle cell is directly dependent on their concentration in the blood. This advantage over glucose is also increased by the fact that fatty acids prevent the assimilation of glucose by the muscular tissue.

This antagonism is quite expedient as it switches the flow of glucose toward the nervous tissue, especially when the reserves of glucose in the organism are not supplemented. In addition, growth hormone counteracts the effect of insulin on the assimilation of glucose. This anti-insulin effect retards still more the utilization of

glucose by the muscular tissue. Therefore, when abstaining from food, the glucose level in the blood decreases and growth hormone, which is freed of "glucose inhibition", switches the organism to the utilization of fat. At the same time, owing to this double antagonism (on the one hand, between fatty acids and glucose, and on the other, between growth hormone and insulin), optimal conditions are created for the catabolism of fatty acids in the muscular tissue, and correspondingly for the decreased utilization of glucose.

All these changes can be expressed by the following old formula: carbohydrates do not burn in the flame of fats. Moreover, when there is a shift toward intensive utilization of fatty acids, the latter increase the production of glucose from protein, i.e., they activate gluconeogenesis, thereby subordinating the activity of the organism to the task of supplying the nervous tissue with energy.

Thus, the organism has two ways of obtaining a supply of energy. According to the first method, which can conditionally be called diurnal, the energy source is supplied with food, at the same time there is a decrease in the utilization of reserve fat. The source of energy in this case is glucose, and to a lesser degree edible fat. The combined utilization of the two energy substrates is facilitated due to the fact that the

fats burn more easily in the flame of carbohydrates.

According to the second method, which can conditionally be called nocturnal, the fatty acids become the principal source of energy. Appropriate alternation between the types of energy sources is achieved by the influence of the food on the four-component energy homeostat system, wherein glucose, insulin, fatty acids, and growth hormone are the basic regulating factors. (In distinguishing this four-component energy homeostat, the author certainly takes into account that many other hormones and factors participate in the regulation of energy processes. But the effect of these additional factors is either similar to that of one of the four components of the energy homeostat, or is achieved by involving these components in the process.)

However, the mechanism of switching over the energy homeostat is disturbed in the process of normal aging. Data obtained in our laboratory indicate that one hour after loading with glucose the concentration of growth hormone in the blood of young subjects decreases by approximately 50%, while in middle-aged people this effect is totally absent (Fig. 5). At the same time, if the supply of carbohydrates does not induce a decrease in the concentration of growth hormone, the organism does not switch from the nocturnal to the diurnal

type of energy supply, i.e., the rhythm of utilizing the energy substrates is disturbed. As a result, the content of fatty acids, glucose and insulin increases more than usual in the blood after a meal, while the utilization of glucose in the muscular tissue decreases. The presence of excess glucose and insulin causes the development of obesity.

It follows that the same changes that are observed in the adaptational and reproductive homeostats occur in the energy homeostat during aging.

But the following may seem strange. If the system is poorly inhibited, i.e., if the increase in the glucose concentration in the blood does not induce normal inhibition of growth hormone secretion, then its level in the blood should increase. However, just the contrary occurs: the growth hormone concentration in the blood of middle-aged people, whose hypothalamic threshold is higher, is clearly lower than in young people (see Fig. 5). This contradiction was unaccountable for a long time until various scientists determined that obesity is characterized by a decrease in the growth hormone level in the blood. It became clear later that it is the fatty acids, whose concentration in the blood is increased in obesity, that induce a decrease in the growth hormone level.

The existence of a "fat inhibitor", based on the inhibiting effect of fatty acids on the secretion of growth hormone is quite expe-

dient. Indeed, if one considers that the intake of food should inhibit the utilization of reserve fat, then, correspondingly, carbohydrates (glucose) and fat (fatty acids)

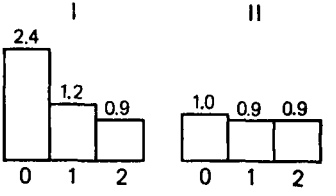

Fig. 5. The effect of age on "glucose inhibition" in humans.

The columns illustrate the concentration of growth hormone in the blood (in ng/ml): 0—prior to intake of 100 grams of glucose; 1—1 hour after intake of glucose; 2—2 hours after intake of glucose; I—healthy young subjects; II—middle-aged healthy subjects.

should suppress the secretion of the fat-mobilizing growth hormone. In other words, the mobilization of fat from the fat depots decreases after the intake of food.

However, there is a significant limitation in the activity of this expedient mechanism that for some reason attracted no attention earlier. During childhood a high level of fatty acids and growth hormone occurs simultaneously in the blood as if there were no "fat inhibitor" in general.

This paradox can be explained as follows. The combined increased concentration of

growth hormone and fatty acids in the blood contradicts their usual interaction, which is determined by negative feedback: the high level of fatty acids in the blood causes the inhibition of growth hormone secretion by acting on the hypothalamus. Therefore, a simultaneous increase in the growth hormone and fatty acid level can occur only if the hypothalamic threshold of sensitivity to the inhibiting effect of fatty acids is increased. In other words, during childhood a phenomenon is observed in the hypothalamus—growth hormone—fatty acid system, which appears in the other principal homeostatic systems only in the process of aging.

Indeed, with age, the hypothalamic threshold to feedback inhibition in the adaptational and reproductive systems increases. The same phenomenon is observed in the energy homeostat in the system controlling the interaction between growth hormone and glucose. But something quite opposite is observed in the same energy homeostat in the course of aging, viz., the age-related decrease in the hypothalamic threshold of sensitivity to the inhibiting effect of fatty acids. As a result of aging, when the fatty acids are the principal source of energy, this causes a decrease in the growth hormone concentration in the blood.

In conclusion, in the course of aging two independent regulatory changes take place

in the energy homeostat: the hypothalamic sensitivity threshold to the inhibitory effect of glucose increases, but the threshold to fatty acids decreases.

But whatever exists in nature exists for a reason. What can induce these opposed changes in such a coordinated energy system?

To grow an organism requires growth hormone and fatty acids that meet the energy requirements of growth. Thus, the fact that during childhood fatty acids do not possess a strong inhibitory effect on the production of growth hormone indicates that this is precisely what is necessary for the growth of the organism.

On the other hand, a glucose inhibitor that operates well in childhood regulates the intake of sources of energy through the appetite centre and, thereby, the distribution of fuel in the system of the energy homeostat, including the diurnal and nocturnal types of energy supply.

When the glucose inhibitor functions correctly, which is observed in children and young people, the switching of the energy flux between glucose and fat is well-controlled. But when the effectiveness of the glucose inhibitor decreases as a consequence of the age-related rise in the hypothalamic threshold, the development of obesity becomes inevitable because of the characteristics of the energy homeostat. In other words, even if there were no age-related

disturbance in the regulation of the appetite, only one change in the hypothalamus-growth hormone-glucose system in the presence of a normal, balanced inflow of sources of energy would gradually lead to switching the energy homeostat to the accumulation of fat. Under these conditions even an insignificant surplus of energy intake over its output (due to age-related disturbances in regulating the appetite) induces obesity.

This is exactly what happens in reality. In this sense obesity is a normal disease that always appears in the process of aging. Just as the climacteric is a natural consequence of age-related changes in the regulation of the reproductive homeostat (Chapter 5), and hyperadaptosis reflects the same in the adaptational homeostat (Chapter 4), age-related obesity is a normal manifestation of age-related changes in the energy homeostat.

However, age-related obesity is not only one of normal diseases. The role of obesity in the development of other diseases is very great. Why does obesity play such an important role?

To answer this question, it is necessary to discuss why obesity, beginning with its onset, "loses all ties with the past" and becomes a self-reproducing process, that is, literally, in "perpetual motion" in the system leading to the development of age-related diseases.

Chapter 8

Obesity: The Disease of Diseases

> Obesity is not the problem of the century, it is a perpetual problem.

Many centuries passed before human beings, after having cognized some of the regularities of nature, started to affect the course of vital processes. The most amazing example of this influence is the prolongation of the average lifespan owing to civilization.

In ancient times, some individuals did live for a long time, but for many centuries, the average lifespan was strikingly short. For example, in France in the fourteenth century it was only 26 years. It was impossible to understand at that time what the true cause of death in humans was, because, as a rule, death was due to external reasons just as it is in wildlife today.

The principal causes of death changed with the advance of civilization.

In the Middle Ages, with the emergence of big cities, mass epidemics of infectious diseases were of catastrophic character. Millions of people died of plague or cholera and only the development of science made it possible to restrain this calamity. Death

from "social diseases" advanced to the first ranks for many years owing to overcrowding and poverty of the majority of the population in the growing cities. Tuberculosis became the scourge of mankind for many years.

Strictly speaking, tuberculosis is an infection, and death from it is considered due to an external cause. At the same time, tuberculosis depends so greatly on social factors that it is, apparently, one of the major diseases of modern civilization.

The significance of "social diseases" increased in time. Overly rich and incorrect nutrition, environmental pollution, and reduced physical activity, and not the infections per se, became the basic causes of these diseases. At the same time, the prevalence of these diseases made it possible for many scientists to advance the thesis of the epidemical character of the diseases of civilization, viz., obesity, atherosclerosis, and cancer.

These diseases certainly have not appeared only in recent years and they are not diseases of modern civilization. There is a well-known ancient fresco that depicts an obese Etruscan who lived two-and-a-half millenia ago.

Nevertheless, as far as human beings are concerned, it must be stated that the increase in the lifespan due to social progress and civilization clearly revealed a trend toward

an increase in adipose tissue with increasing age. This problem is to a considerable extent a biological one. Not only humans, but also animals demonstrate fat accumulation with increasing age.

What determines the stability of age-related obesity and its tendency to progress? If obesity develops in the course of normal aging, i.e., according to rules dictated by the law of deviation from homeostasis, then its onset is associated with a disturbance in the regulation of the appetite (Chapter 6), with a disturbance in the regulation of the diurnal and nocturnal types of energy supply (Chapter 7), and with hyperadaptosis (Chapter 4). In the final end, these mechanisms induce the accumulation of surplus fat. Apparently, the quantity of adipose cells in adults is constant. Therefore, the existing adipose cells begin to overfill with fat as the fat mass increases. The accumulation of fat increases the volume of the adipose cell and, correspondingly, its surface area, and it decreases the sensitivity of adipose tissue to insulin.

Numerous recent studies have shown that the quantity of insulin receptors on the membrane of an adipose cell that is overfilled with fat (such as on the membrane of lymphocytes in obesity) is several times less than in normal cells and, consequently, the effectiveness of insulin is also decreased. The organism responds by an addition-

al, compensatory increase in the production of insulin. This increase in the insulin level is manifested quite peculiarly at certain stages in the development of obesity. Insulin transforms glucose into fat and also inhibits the utilization of fat. Being a hormone of the diurnal type of energy supply, insulin prevents the switching on of the nocturnal type of energy supply. Therefore, an obese person, despite his or her reserves of fat, often experiences an acute sense of hunger. Owing to surplus insulin, the organism behaves like the greedy Gobseck who was busy with hoarding: it accumulates fat but doesn't want to spend it.

However, the "pumping up" of the adipose cells with fat cannot continue indefinitely. When the adipose cells are overloaded with fat, they begin to return it to the organism in the form of fuel, i.e., fatty acids. Indeed, though the surplus of insulin, which is characteristic of obesity, prevents the mobilization of fat, the concentration of fatty acids in the blood still increases. This means that, in overcoming the counteraction of insulin, the adipose cells release more fatty acids (as compared to the norm) into the blood. The fatty acids are rapidly carried away to the tissues where they are utilized as fuel. Half of the fatty acids circulating in the blood reach the cells within four to six minutes.

In accordance with the antagonism between the diurnal and nocturnal types of energy supply, the increased utilization of fatty acids creates a "fat obstacle" in the utilization of glucose. Therefore, the diurnal type of energy supply does not function properly in obese people. When encountering a "fat obstacle" in the muscular tissue, the blood glucose rushes to the adipose tissue and liver where it is engaged in the synthesis of fat.

This is the reason why in obesity the organism draws energy from fatty acids in the daytime as well as in the nighttime. A certain "transshipping point" is created in the organism where the glucose is first turned into fat, and then the fatty acids are spent to supply the organism with energy. As a result, the organism gradually shifts to an energy supply based on fat. (Continuous indirect calorimetry made it possible for a number of researchers to show that the oxidation of fatty acids increases in obese humans.) Fat burns in the furnace of the organism day and night. Therefore, when carbohydrates (glucose) and fats enter the organism with the food, under the conditions of a fat-based energy supply they contribute to the accumulation of adipose deposits, which, in their turn, support the fat-based energy supply, and so on.

Thus, a vicious metabolic circle is formed which stabilizes obesity in the orga-

nism. Simultaneously, the second stabilizer of obesity switches on. The surplus supply of fatty acids that penetrates into the blood as if through the pores of an overfilled ceramic vessel induces a decrease in the growth hormone concentration in the blood. The physiological significance of this mechanism is clear. If the energy requirements are satisfied owing to an increase in the fatty acid concentration, a high concentration of the fat-mobilizing factor—growth hormone—becomes surplus and, therefore, the "fat inhibitor" eliminates the effect of this factor.

But let's recall that it is precisely the increase in the concentration of growth hormone in the blood that is the first step toward the development of obesity. It would seem, therefore, that a decrease in growth hormone, which is induced by surplus fat, should eliminate disturbances in the energy system of the organism. However, no normalization in the energy system occurs despite the elimination of the primary disturbance. Why is this so?

The increase in the fatty acid concentration in the blood induces reduced utilization of glucose by the muscular tissue. As was emphasized earlier, the antagonism between the utilization of fatty acids and glucose, or between the nocturnal and diurnal types of energy supply, automatically starts to operate. As a result, glucose,

which has not been assimilated by the muscular tissue, accumulates in the blood after the intake of food. Since glucose stimulates the release of insulin (the hormone promoting the utilization of glucose), under these conditions the concentration of insulin exceeds the norm. However, the "fat obstacle" in the uptake of glucose by the muscle cells directs it to the adipose tissue where the glucose transforms into fat under the influence of insulin. Thus the fatty acids that have been consumed are replenished, thereby ensuring a continuous supply of fatty acids into the blood for burning in the muscular tissue. In other words, a self-supporting cycle is formed (a fat shunt), creating a constant shift toward the fat-based mechanism of supplying the organism with energy.

It can be stated that the four-component design of the energy homeostat functions in obesity without one component, viz., growth hormone. Figuratively speaking, an obese person is a beheaded horseman because the central hypothalamic component of the energy system is switched off, and this failure in regulation disturbs the natural rhythm of switching over the energy system. Obesity stabilizes and with increasing age the person gradually shifts to the fat-based energy supply.

The most amazing point in all this is the fact that the "fat inhibitor", which

switches off correct utilization of fuel, comes into existence at a very young age. For example, the concentration of growth hormone in a healthy human decreases between the ages of 20 and 39. This means that the "fat inhibitor" operates in full force at this age. But even this is still not the very beginning of "energy aging".

A recent publication describes an experiment during which 21 to 26-year-old students were injected with nicotinic acid, a vitamin that inhibits the mobilization of fat. The concentration of growth hormone in their blood increased by more than twofold. This means that the "fat inhibitor" is operative even at this young age.

It can be assumed that the accumulation of surplus fat, which creates the "fat inhibitor", begins immediately after the cessation of the organism's growth and development. In this sense the accumulation of fat, which inhibits the secretion of growth hormone, may be one of the factors that switch off the growth-stimulating influence of growth hormone and, at the same time, the mechanism that switches the organism to the fat-based energy supply.

It has been calculated that the accumulation of four to five kilograms of surplus fat in the organism creates a dangerous shift in metabolism, which is sufficient for the development of atherosclerosis. Indirect calculations indicate that this superficial-

ly minor weight gain is realized by the age of thirty if one considers the beginning of the countdown to be the age of twenty. But the key role of obesity in the formation of age-related pathology is also determined by many other factors, which are outlined below.

First of all, a reserve of potential energy is created in the form of fat, which determines the basic feature of age-related diseases, viz., their development due to the intensification of normal physiological processes. The key role is performed by the relationship between obesity and the increased level of insulin in the blood.

Obesity and insulin make an "inseparable couple". This alliance is so essential that it is revealed even at the earlier stages of an organism's development and, apparently, of the evolution of an organism as a whole. The fact is that, alongside insulin, there are also insulin-like substances in the organism, or, as they are called, somatomedins, which mediate the effect of growth hormone. The concentration of somatomedins increases in obesity, while their surplus contributes to the development of atherosclerosis (Chapter 9) and cancer (Chapter 10).*

* In particular, cholesterol synthesis increases in proportion to the increase in the body size, which is expressed by the body mass or its surface area. This association is preserved in obesity even in

Second, obesity reduces the effectiveness of immunological protection (Chapter 9).

Third, obesity creates conditions for the onset of type II diabetes mellitus, or, to be more precise, it induces a specific condition, viz., a decrease in the utilization of glucose as fuel. The age-related decrease in the rate of utilizing glucose and type II diabetes mellitus are not quite identical though obesity contributes to the development of both these conditions. The age-related decrease in the rate of utilizing glucose and the increase in the level of postprandial reactive insulin take place in everyone, while type II diabetes mellitus, i.e., diabetes mellitus that develops despite the surplus of insulin in the blood, is a frequently encountered, but not obligatory (normal), disease.

The fourth factor is that obesity contributes to the onset of hypertension, in particular, due to the fact that insulin "retains" sodium in the organism.

The fifth factor is that obesity contributes to the "gluing" together (aggregation) of thrombocytes, which increases the proba-

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middle age. In light of this, the widely accepted assertion that in humans the synthesis of cholesterol decreases with increasing age seems doubtful. Apparently, the data obtained in experiments with rodents or in *in vitro* experiments (i.e., outside the organism) are insufficiently informative.

bility of thrombosis, and, in the presence of cancer, its dissemination.

The sixth factor is that obesity diminishes the activity of the thyroid gland which, in its turn, contributes to the onset of atherosclerosis and cholelithiasis.

The seventh factor, viz., the shift to the preferable utilization of fatty acids as fuel, which is characteristic of obesity, is the common factor that makes obesity related to the mechanisms functioning in the early stages of the organism's development during pregnancy (Chapters 3 and 14), and to the mechanisms by which the organism counteracts the unfavourable influence of the external environment, e.g., stress (Chapter 2). This same shift determines the wide-scale relations between obesity and accelerated development (Chapter 14).

Finally, owing to the fact that obesity may also arise in persons whose regulatory systems are sound, as a consequence of overeating, which supplies the organism with more energy than it can consume, obesity is a highly widespread disease. In addition, obesity due to such causes creates the same disturbances in the organism that are characteristic of obesity due to internal causes.

What happens in the organism as a consequence of obesity occurs on a broad scale, though, in essence, only two factors are responsible, viz., surplus insulin and surplus

fatty acids, or, to be more precise, the combined effect of these two factors.

The unfavourable effect of obesity is manifested most vividly when the period of reproduction terminates. Then, obesity plays a fatal role, tying the processes of aging and age-related diseases into one knot (Chapter 11). This is the reason why obesity is not a problem of the century, but a perpetual problem. Hence, it is the disease of diseases.

Chapter 9

Atherosclerosis and Metabolic Immunodepression

> Atherosclerosis and age-related decline in immunity are as ancient as the world itself because the basis for their development is the mechanism ensuring the reproduction of cells and growth of the organism.

Atherosclerosis and associated complications are the basic cause of death in industrially developed countries. The excessive supply of cholesterol in the organism together with food contributes to the development of atherosclerosis. This has been established in so-called epidemiological studies examining the diet in different regions with a high and relatively low incidence of atherosclerosis.

However, in recent years the role of surplus cholesterol in the development of atherosclerosis has been frequently questioned in the popular scientific literature. Publications addressing this problem usually appeared as additional details about the process were established when studying the mechanism of the onset of this disease: in particular, the mechanism governing the uptake of cholesterol into the cell and its removal (the carriers of cholesterol in this case are various compounds that will be discussed below) has been studied most in-

tensively. In addition, when the walls of vessels are damaged, for example, by certain viruses, surplus cholesterol can also accumulate despite its normal content in the blood. But, given unperturbed conditions, the old thesis remains invariable, i.e., the higher the concentration of cholesterol in the blood, the higher is the probability of the development of atherosclerosis. (For example, individuals suffering from an inherited disease characterized by an increased concentration of cholesterol in the blood—homozygous family hypercholesterinaemia—fall ill with serious atherosclerosis in their childhood.) In turn, the level of cholesterol in the blood is determined by its synthesis, metabolism, and destruction in the organism, as well as by how much is taken in with the food.

During youth the excessive intake of cholesterol with food induces a decrease in its production in the liver; therefore, the total "cholesterol balance" is maintained in the organism. But over the course of years, this mechanism of self-regulation is apparently disturbed, and the excessive intake of cholesterol with food of animal origin (meat, milk, butter, egg yolk) does not lead to a decrease in its concentration in the blood. On the contrary, the concentration of cholesterol in the blood rises due to blocking of the lipoprotein receptors in the liver.

However, the problem of atherosclerosis would not be so serious if everything were determined by the type of diet. The complexity of this problem is associated, first of all, with the fact that there are internal factors in the organism that determine the age-related rise in the cholesterol concentration in the blood.

As was mentioned in the chapter on the law of deviation from homeostasis, during certain periods of ontogenesis an increased concentration of cholesterol is necessary to ensure increased cell division. This is necessary during childhood, a period of intensive growth, and in the female organism, during pregnancy. Additional synthesis of cholesterol is ensured in both cases (as in the Pacific salmon during spawning) because of the decreased utilization of glucose as a fuel and the development of obesity, i.e., because the organism switches over to the more advantageous source of energy supply—fat. Hence, "fat energy" is necessary both for the fetus, and for the child during the stage of growth.

But in the process of natural selection, living nature does not relinquish its acquisitions that maintain the life of the species even if these acquisitions play an unfavourable role when the organism reaches maturity. Therefore, if obesity commences without being associated with the organism's requirements for growth (e.g., as a

result of overeating, decrease in physical activity, or, more importantly, age-related changes in homeostasis), the production of cholesterol by the liver increases as well.

In Chapters 6 and 7 we discussed the mechanisms of the development of age-related obesity. Now we shall try to examine why obesity increases cholesterol level in the blood and why this leads to the accumulation of cholesterol in the cells and tissues, inducing various diseases, most importantly atherosclerosis.

When the organism takes in more food than necessary, the content of glucose increases in the blood. Also, during the process of normal aging (Chapter 11), the rate of glucose utilization decreases. The surplus glucose cannot be completely metabolized all at once because the capacity of the energy furnace is limited. Hence, the surplus glucose stimulates a surplus secretion of insulin into the blood. A large amount of triglycerides (i.e., fats) and cholesterol is formed from the products of glucose and fatty acids in the liver under the influence of the surplus insulin. Since both these products are not water-soluble, they are unable to leave the liver independently. A more complex aggregate is formed in the liver, containing carrier-proteins (apoproteins) for triglycerides and cholesterol. These particles are called lipoproteins.

Triglycerides and cholesterol leave the liver complexed to one of the classes of lipoproteins—the very low-density lipoproteins (VLDL). The VLDL are subjected to changes in the vessel bed as a result of which the greater part of cholesterol from the remaining VLDL is transferred by means of enzymes and cell membrane receptors to low-density lipoproteins (LDL). The receptors transport LDL into the cells where free cholesterol becomes part of the framework of the cells' membranes. Thus, the development of obesity meets the requirements for cholesterol during the organism's growth and development.

But when obesity begins to develop in an organism that has completed its growth, surplus cholesterol enters cells that are not dividing as actively as earlier. These are the cells that make up the walls of the blood vessels. As a result of the specific characteristics of the uptake of cholesterol by these cells, the cholesterol concentration in the vascular walls increases in parallel to the increase in the concentration of LDL in the blood. (There are several mechanisms that supply cholesterol to the cells: through LDL receptors; by transport into the cell along the concentration gradient; through unregulated endocytosis; and more rarely by phagocytosis of VLDL and LDL, e.g., by macrophages.) The surplus cholesterol begins to accumulate in the vascular

wall, paving the way for the disease called "atherosclerosis".*

Though the amount of cholesterol in the walls of large arteries and aorta increases parallel to the increase in the cholesterol concentration in the blood, which, in essence, characterizes atherosclerosis, the clinical complications of this process are greatly associated with focal lesions that are most often conditioned by the development of atherosclerotic plaque.

It has only recently been determined that at the centre of each atherosclerotic plaque there is an accumulation of smooth muscle cells that form the framework of large vessels alongside the connective tissue. It is believed that each individual plaque comes from one ancestral muscle cell. In essence, an atherosclerotic plaque is a benign muscular tumour. Accordingly, it is assumed that herpes viruses, or chemical carcinogens may cause the development of an atherosclerotic plaque. The role of various injuries to the walls of the blood vessels is also quite significant, because growth factors are released from the thrombocytes when the injuries are being repaired, and

* The medical classification of diseases associated with atherosclerosis is based on clinical symptoms of the disease, e.g., myocardial ischemia, vascular injury of the brain. In this discussion only the biological regularities in the development of atherosclerosis are addressed.

these factors may condition excessive stimulation of cell division in the tissues of the vessels. Finally, metabolic and hormonal factors, i.e., an increase in the concentration of insulin, somatomedins, and cholesterol (LDL), also contribute to increased cell division in the vascular walls and to excessive "sticking" of the thrombocytes.

The result is an atherosclerotic plaque with layers of muscle cells, endothelia, collagen, macrophages (foam cells), lipids (cholesterol ester), and calcium deposits. Finally, as a consequence of the excessive synthesis of triglycerides and cholesterol in the liver, the structure of the carrier-proteins (apoproteins) can change, which leads to an increased supply of LDL particles reaching the vascular walls via immunological mechanism.

We see here that a vitally significant process that ensures cell division is at the basis of the onset of atherosclerosis, but this physiological mechanism now functions incorrectly and excessively.

The point should be made that the organism is not so defenceless in regard to atherosclerosis. In the first place, in addition to the lipoproteins that transport cholesterol into the cell (VLDL and LDL), there are high-density lipoproteins (HDL) that remove surplus cholesterol from the cell. True, it has been determined that the production of the HDL precursor in the liver decreases if

there is a decrease in physical activity or if the fat mass and concentration of triglycerides in the blood increase, which is commonly observed with the advance of age and in the case of obesity. When considering everything stated above, viz., the dependence of the development of atherosclerosis (especially its complications) on the complexes of factors, it becomes clear that an increase or decrease in the cholesterol concentration in the blood cannot in each individual case accurately characterize the risk of onset of atherosclerosis and reflects the probability of this risk only when there is a large number of observations.

The immune system is the second barrier of protection against atherosclerosis. This multicomplex system includes, among others, macrophages, or, as they are sometimes called, "garbage collectors". By means of phagocytosis (engulfment) which was discovered by I. I. Mechnikov, these cells eliminate dead cells and various large particles (e.g., microbes and fat "droplets"). It was observed long ago that macrophages overloaded with fat transform into foam cells and are unable to "transport" their cargo to the lymphatic ducts.

These macrophages "poisoned" with fat may make up one of the components of the phenomenon qualified as metabolic immunodepression. To understand the origin of this phenomenon, it is necessary to focus

once again on some mechanisms originating during pregnancy.

Two tasks of the organism that ensure pregnancy are associated with this problem. One of these tasks is to create conditions for the rapid increase in the mass of fetal cells. As mentioned above this task is solved by shifting the organism to an energy supply, based on the metabolism of fat, which ensures the necessary synthesis of cholesterol for building cell membranes. The second task is reduced to the necessity of suppressing cellular (transplantation) immunity. Let's discuss this in greater detail.

The immune system, which, as is commonly stated, discriminates "self" from what is "foreign", came into existence at a certain stage of evolution. At first it was thought that the immune system protects the organism only against the penetration of microbes and viruses. By discriminating the microbe from its own proteins, the system can apply two mechanisms of protection. According to one mechanism, white blood corpuscles—lymphocytes (or, to be more precise, their descendants, the plasmocytes)—produce defense proteins called antibodies, which have an "affinity" for the strange proteins of the microbe and, as a result, neutralize them. Lymphocytes that are associated with the production of antibodies are called B-lymphocytes. They are

the major carriers of so-called humoral immunity. The antibodies are distributed throughout the organism by the blood circulation.

The second mechanism of protection is cellular immunity. It is effected directly by the immune cells called thymus-dependent lymphocytes, or T-lymphocytes. In turn, the T-lymphocytes are divided into several subgroups, including memory lymphocytes, helper lymphocytes and suppressor lymphocytes (T-suppressors) which suppress the activity of B-lymphocytes.

Finally, it is necessary to mention in this brief enumeration the major working factors of the immune system called A-cells, or macrophages, i.e., devourer cells. The three basic systems of immunity, viz., cellular, humoral, and A-cells, are in complex interaction, releasing special substances that coordinate their work.

The proteins that form the structural and functional base of each cell have a set of "building blocks" that differ from each other both quantitatively and qualitatively although they are made up of the same components in all living beings. These differences define the individual composition of each species of living organisms, and the specific features of each individual within a species. Therefore, each organism is unique and inimitable. Tissue incompatibility is a consequence of this phenomenon.

In addition, when the memory lymphocytes are still in the embryonal stage they "memorize" the proteins of their own body once and for all, recognizing them as their own. In essence, this property of the immune system is a major one for preserving constancy of the internal environment in the organism. It does not matter whether the activity of the immune system is directed against tissues, bacteria, viruses, fungi, damaged tissues in the body proper, or, finally, against the changed properties of the body's cells (which occurs in malignant transformation); in all cases its purpose is to preserve the constancy of the body's composition. Protection against bacteria and certain viruses is effected mainly by humoral immunity, or by the B-lymphocytes, while foreign cells are removed by cellular, or transplantation, immunity (T-lymphocytes). Macrophages also function in both cases at various stages of immunological protection.

A fertilized ovum possesses not only the properties (heredity) of the maternal organism, i.e., "of its own organism", but also the heredity of the paternal organism, i.e., "of a foreign organism". This cell is a peculiar type of foreign transplant. The alloy of what is "self" and what is "foreign" is recognized by the immune system. According to the laws of cellular, or transplantation, immunity, the fetus should be reject-

ed by the maternal organism. Why doesn't this occur? Although there are several theories as to how the fetus is protected from attack by the immune system, we shall discuss a new theory, which takes into consideration the phenomenon of metabolic immunodepression.

As is generally known, the immune system interacts with the other basic homeostatic systems, primarily, with the adaptational and energy ones. As was mentioned above, cortisol, the basic protective hormone whose production increases sharply under stressful conditions, provides antistress protection and induces immunodepression.* On the other hand, one of the basic elements of the energy homeostat—growth hormone—also stimulates the immune system under certain conditions.

The influence of certain hormones on the immune system has been known for about 30 years. But only recently it became clear that fat suppresses immunity.

First, it was found that some of the prostaglandins, which are compounds derived from unsaturated fatty acids (i.e., liquid vegetable oil), suppress the immune system. However, later it became clear that the

* The concentration of cortisol also increases when antigens enter the organism. The hormones of the lymphocytes transmit appropriate signals to the hypothalamus, which specifically increases the level of ACTH, a hormone stimulating the secretion of cortisol.

immune system is always suppressed when there is a shift in the organism towards the intensive utilization of fatty acids as fuel (both saturated and unsaturated fatty acids), and that this suppression bears no relation to the formation of prostaglandins.

Before considering which metabolic factors induce immunodepression, let's recur once again to the role of T-lymphocytes in cellular immunity. Mostly mature lymphocytes circulate in the blood. If T-lymphocytes are compared with erythrocytes, a certain injustice in the "distribution of labour" is evident. Erythrocytes work tirelessly, transporting oxygen to the tissues, while the lymphocytes seem to travel in the organism in a care-free manner. However, this inactivity is only seeming: the lymphocytes are calm only until the "enemy" reveals itself, which is everything that is foreign and differs from the organism that is host to the lymphocyte.

T-lymphocytes possess an amazing property. When there is no threat, they behave like common cells: they live, age, and die. But when the membrane of the T-lymphocyte registers that some "foreign" proteins have appeared, a series of striking transformations occurs, as a result of which the mature lymphocyte is rejuvenated and soon reacquires the ability to divide. If the "enemy" remains detectable, each new cell that appears soon begins the cycle of divi-

sion. As a result, the number of cells progressively increases and the "enemy" is confronted by a powerful attack on the part of the growing armada of lymphocytes.

The mature lymphocyte's capacity for division is similar to the continuous fission potential in an amoeba. The difference is only that in the amoeba nutrition stimulates fission, while in the case of a lymphocyte, the stimulus comes from the environment where the "enemy"—the foreign protein (antigen)—is detected.

But for the potentially immortal amoeba, the environment is of primary, truly vital, significance, because its true lifespan depends on external factors. When toxic substances accumulate in the environment, they can cause the immediate death of all the generations of unicellular organism. But if the amoeba's habitat is its environment, the habitat of lymphocytes is the host organism, first and foremost, the blood and lymph. Continuing this analogy, it can be assumed that the life and death of T-lymphocytes, as in the case of the amoeba, is determined by the habitat. The accumulation of toxic substances in the blood and lymph can cause intoxication of the lymphocytes, resulting in the loss of the capacity for division.

When the concentration of fatty acids, cholesterol, and, possibly, insulin (i.e., the whole complex of vitally necessary sub-

stances) increases in the blood above all limits, they become the toxic substances that limit division and, consequently, the life of T-lymphocytes. Each of these factors plays a specific role.

When the organism switches over to an energy source based on fats, the fatty acids switch on the mechanism of glucose production (gluconeogenesis). This is achieved not only through the activation of the enzyme systems by fatty acids, which transforms amino acids (proteins) into glucose (i.e., activates gluconeogenesis), but also through suppyling the necessary amino acids, which contributes to the destruction of T-lymphocytes.

As far as cholesterol is concerned, it enters the lymphocyte, as it enters any other cell, mainly complexed with low-density lipoproteins. But when a surplus of cholesterol accumulates in the lymphocyte membrane, the membrane becomes less elastic and its capacity to perceive the signals arising from antigens (mitogens) and growth factors decreases, or is lost entirely. As a result, the lymphocyte capacity for division decreases, or is lost. And if the quantity of T-lymphocytes does not increase as expected with the appearance of the "enemy", antigen, then many, if not all, of the reactions of cellular immunity suffer. Indeed, research carried out at our laboratory indicates that normalization of the

composition of the internal environment (and, correspondingly, an improvement in the immune indices) combines with the decreased concentration of cholesterol in the lymphocytes and the recovery of their capacity for division.

The accumulation of cholesterol in the lymphocytes, which occurs during aging, is not a simple process. Just as mechanisms for maintaining stability (homeostasis) exist in the organism as a whole, similar mechanisms function in each cell of the body. For example, if cholesterol enters a cell from the blood, then the synthesis of cholesterol in the cell decreases and, as a consequence, equilibrium recovers. Therefore, if the concentration of cholesterol in the membrane of lymphocytes increases with increasing age, it means that the homeostasis of the cell is disturbed for some reason. As far as a disturbance in the cell's cholesterol homeostasis depends on the factors of the internal environment, it follows that the metabolic shifts associated with an increase in the concentrations of glucose, cholesterol, triglycerides, fatty acids, and insulin in the blood condition the accumulation of cholesterol in the lymphocytes.

Finally, an elevation in the insulin level in the blood decreases the number of insulin receptors and, as a result, the sensitivity of the lymphocyte to insulin, the hormone that is necessary for the assimilation of

glucose. This, in turn, drives the lymphocyte to switch over to the extremely dangerous fat-based mode of nutrition. All together this causes a decrease in the activity of cellular immunity, i.e., a decrease induced by metabolic factors. Therefore, the author has designated this phenomenon, or newly discriminated normal disease, as metabolic immunodepression.

Hence, the onset of metabolic immunodepression should occur whenever there is a shift toward the intensive utilization of fatty acids instead of glucose as a fuel. This situation also arises during pregnancy. The elevation in the level of fatty acids, LDL (cholesterol), and insulin in the blood in pregnancy, suppresses cellular immunity and is therefore apparently one of the defensive factors that prevents rejection of the fetus as a foreign transplant.

Thus, a shift during pregnancy to the fat-based mode of energy supply creates, on the one hand, metabolic conditions for the rapid increase in the cellular mass of the fetus (which is met, in particular, by an increased synthesis of cholesterol) and, on the other hand, suppresses the activity of cellular (transplantation) immunity (which, in turn, contributes to an increase in the cholesterol concentration in the blood). Hence, two cardinal problems that are related to an organism's development are simultaneously solved.

It should be stressed that metabolic immunodepression affects cellular but not humoral immunity. If it were otherwise, i.e., if the metabolic factors depressed the activity of all parts of the immune system, then the suppression of humoral immunity, which is directed mainly to counteract the development of infections, would make the organism highly vulnerable during pregnancy. This would be incompatible with the strategy of life which lies in finding optimal methods in the process of evolution for solving problems that are related to the development of the organism.

The selective influence of metabolism on immunity is realized owing to the fact that the suppressor-lymphocytes discussed above relate to the class of T-lymphocytes. It is the activity of the T-lymphocytes that is suppressed by the "fat-based energy", and since the T-suppressors inhibit the activity of B-lymphocytes, which produce antibodies against microbes, humoral immunity does not suffer in the presence of metabolic immunodepression. On the contrary, the activity of humoral immunity frequently increases under these conditions, which in certain cases results in adverse consequences, contributing to the development of so-called auto-immune diseases such as those affecting the joints. Therefore, in particular, with increasing age, the occurrence of antibodies to one's own tissues increases along

with the decrease in cellular (transplantation) immunity, and this is one of the essential factors in the age-related increase in the incidence of auto-immune diseases.

Thus, the onset of metabolic immunodepression as a "normal disease of pregnancy" is biologically expedient.

But this mechanism starts to function also in any type of obesity that is not associated with pregnancy. It is observed in normal aging, which we shall discuss below (Chapter 11); in chronic stress, when immunological protection decreases and there is a frequent onset of chronic diseases; in diabetes mellitus, which is frequently accompanied by infectious processes; and in atherosclerosis, when metabolic immunodepression makes it difficult for the "garbage-collecting" macrophages to remove surplus fat and cholesterol from the vessels.

Metabolic immunodepression facilitates recovery and even normalization of immunity. In contrast to the assertion that the age-related decrease in cellular immunity is supposedly conditioned by exhaustion or a disturbance in the activity of the parent (trunk) immune cells that form the T-lymphocytes circulating in the organism, it is now possible to speak of the role of functional (metabolic) factors in the age-related decrease in this type of immunity.

This conclusion does not contradict the role of other factors in the age-related de-

crease in immunity, for example, those associated with a decrease in the production of thymus hormones. And what is more, it can be assumed that the elimination of metabolic immunodepression may contribute to the more effective influence of these hormones. As far as the affection, or exhaustion, of the reserve immune cells is concerned, these phenomena apparently do play a role, but this occurs much later after the beginning of metabolic immunodepression. The ways of normalizing are discussed in a special chapter, but here it is worth noting that living nature itself "knows" of the functional (i.e., reversible under certain conditions) character of metabolic immunodepression. The instinctive loss of appetite during many diseases apparently increases the immunobiological protection of the organism because of the temporary termination of the fat supply. (Though the utilization of fat from the depots of the organism increases when abstaining from food, the level of insulin and cholesterol in the blood drops, i.e., the influence of two major components of metabolic immunodepression is eliminated. Therefore, cellular immunity improves during short-term abstention from food.)

In this chapter an attempt was made to determine what unites atherosclerosis and metabolic immunodepression with one another as well as with the mechanisms of

growth and development of the organism. In other words, atherosclerosis and metabolic immunodepression exist as diseases because the previous mechanism of their formation served the purpose of the organism's growth and development as well as repair of damaged cells. However, the deviation of homeostasis that occurs during normal aging switches on these mechanisms when they are no longer necessary, or sharply increases their activity, such as when repairing injuries of the vascular wall. As a result, these expedient physiological mechanisms begin to form pathologic processes.

It is certainly difficult for the author to substantiate the thesis that *everything* that contributes to the onset of metabolic immunodepression and atherosclerosis also creates conditions for the onset of cancer. But the latter problem will be discussed in the next chapter.

Chapter 10

Cancer and Cancrophilia

It will never be possible to completely prevent the development of cancer but it is quite realistic to eliminate it as a disease. This contradiction reveals the difference and relationship between the probabilistic and natural events in the development of cancer.

Under experimental conditions cancer cells can be transplanted from one organism to another, thus maintaining the existence of a tumour for a much longer period than the life of the organism where they originated. Therefore, it can be determined that the basic difference betwen a cancer cell and a normal cell consists in the following: a malignant cell is potentially immortal, while a normal cell, under similar experimental conditions, can live and reproduce for a specific and strictly limited period of time.* It is as if a malignant cell becomes an organism without internal causes of death, whose lifespan is dependent on the conditions of the habitat as it is in some species of protozoa. Consequently, the mechanism of malignant transformation is sealed in the heredity apparatus of the cell,

* Sex cells, which transmit genetic information throughout the entire period of evolution of a species, are still an inexplicable exception.

i.e., cancer is first and foremost a cellular problem.

Our knowledge concerning cancer has increased greatly during the last few years. Many general and scientific publications have appeared about the impending solution of the problem of the origin of cancer, and, possibly, of its treatment. What has happened in this aspect?

The reader should be reminded that modern medicine originated first of all as ecological medicine. Accordingly, for many years, the search was on to find the external causes for the development of cancer. As a result of this laborious work it has been determined that the following agents can induce cancer: 1) some chemical substances (which were designated by the term "carcinogen", i.e., "cancer-producing"; 2) ionizing radiation, ultra-violet rays, and even sunlight, which can increase the incidence of carcinoma cutaneum and melanoma (a type of tumour made up of cells, birthmarks); 3) a series of hormones, e.g., female sex hormones; 4) inert materials, e.g., plastics plates and certain types of asbestos fibres; and 5) certain viruses. The most amazing thing is that all these different agents, which seemingly have nothing in common, can cause the transformation of normal cells into cancerous ones that are characterized by common properties irregardless of the origin of this transformation.

It follows that different agents that cause malignant transformation of the cell somehow change its genetic apparatus. In recent years, investigations of these changes have brought outstanding researchers to unexpected and very important results. First, it became possible to determine that the genomes of viruses that cause malignant transformation of the cells contain genes directly responsible for this transformation. Gradually more than twenty genes were identified, forming a family of oncogenes, i.e., genes inducing an oncological process.* In light of these data, the viral-genetic hypothesis of the Soviet scientist L.A. Zilber was confirmed, according to which the integration of the viral genome into the genome of a normal cell can induce its malignant transformation. At the same time, the original version of the "virus theory" does not explain the development of cancer under the influence of other non-viral agents, e.g., chemical carcinogens. The general picture became clearer when it was shown that every normal cell (in all the investigated species, rang-

* Malignant tumours are commonly divided into two broad categories according to the origin of the initial (normal) cells: carcinoma is made up of epithelial cells; and sarcoma is made up of connective tissue cells. Malignant processes in the hematopoietic system belong to a separate group.

ing from yeasts and drosophila to humans) contains genes that are similar to viral oncogenes. Correspondingly, cellular oncogenes are called protooncogenes.*

The discovery of cellular oncogenes made it possible to explain the role of external agents such as chemical carcinogens in the onset of cancer as follows. Oncogenes do not function in a normal cell, or, to be more precise, they function in a strictly controlled mode, e.g., oncogenes c-myc and c-fcs become active during each cell division. At the same time, harmful external as well as internal agents (such as free radicals) can accidentally cause such impairment of the cellular genome that induces permanent activation of the oncogenes.**

Today, several mechanisms are known leading to the activation of oncogenes as a

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* There are arguments in favour of the fact that it was not the viral oncogene that was once incorporated into the cellular set of genes, i.e., the genome, but on the contrary, certain viruses "snatched away" and "included" into their structure certain cellular genes that performed the role of viral oncogenes when these viruses entered the cells and again became incorporated into the cell genomes. Therefore, the cellular oncogene is designated with the prefix "proto", meaning "first".

**The malignant transformation of the cell is realized in many cases by the action of at least two oncogenes. Moreover, the property of "potential immortality" and the property of malignant growth are ensured by different oncogenes.

result of impairment of the genetic apparatus. The basic mechanisms are as follows: 1) translocation (displacement) of a gene or a group of genes from one chromosome to another, where the oncogene not only escapes the control of the blocker but is also influenced by the activating (promoter) gene. For example, during the development of one type of lymphoma, the cell oncogene from chromosome 8 enters chromosome 14, and at this new site the oncogene is subjected to continuous stimulation by the regulatory (promoter) gene that normally controls the rate of antibody production; 2) transposition of the oncogene, i.e., its displacement within the same chromosome, which leads to the activation described above; 3) amplification (multiplication of one and the same gene), which increases the dose of coded oncoproteins; 4) integration of the viral oncogene into the cell genome, or viral impairment of the genetic apparatus; 5) so-called point mutation resulting from the replacement of one amino acid in the oncoprotein, e.g., replacement of the amino acid glycine by valine in oncoprotein p21 in position 12 changes the properties of the oncoprotein (see below); 6) decrease in the degree of DNA methylation, which depends not on the change in the DNA-oncogene structure, but on the disturbance in the methylating mechanisms controlled by other genes.

The activation of genes and oncogenes, no matter how it has been induced, leads, as is known, in the final end to increased synthesis of the protein products of gene activity, which in conformity with the activity of the oncogenes have been designated as transforming proteins or oncoproteins. Naturally, immediately after the discovery of oncogenes a question arose as to how various oncoproteins, which are coded for by various oncogenes, could effect the malignant transformation of a cell. The greatest attention was given to the oncoprotein pp60, which was coded for by the viral oncogene of sarcoma Rousa (oncogene V-52c), because in this case malignant transformation of the cells is achieved by only one oncogene and, consequently, one oncoprotein. In addition, oncoprotein pp60, as it turned out, possessed enzymatic activity characteristic of tyrosinekinase and, consequently, the influence of this oncoprotein-enzyme could spread to various cellular systems. Therefore, a series of hypotheses soon appeared on the mechanism of malignant transformation induced by oncogene pp60. We also advanced a hypothesis (V.M. Dilman and M.V. Blagosklonny, *Problems of Oncology*, 1980, 6), which, as distinct from other hypotheses, was based on endocrinology. The initial ideas of our hypothesis can be considered and compared with the subsequent events that occurred when studying the

mechanisms of malignant transformation only after first discussing some endocrinological problems that are related to how the cancer cell is supplied with energy substrates.

First of all, it should be noted that the existence of oncogenes in each cell (which is an example of amazingly conservative preservation for almost two billion years of evolution if it is determined by the conjectural time of the origin of yeasts, in which oncogenes have also been found) would be impossible if they did not play an important role in the activity of the normal cell.

We did not know what this role was, but, as applied to cells, including malignant cells that receive nutritious substances (primarily glucose from the internal environment of the organism), we considered the situation in which oncogenes and, correspondingly, oncoproteins could play an essential role.

As is known, each cell needs glucose but glucose is unable to penetrate the cell without the aid of special protein carriers. In their turn, the synthesis and functioning of these carriers is controlled by hormones, primarily insulin, which brings about its effect by activating the enzyme of its membrane receptor. In the absence of insulin, glucose transport practically ceases. Insulin also stimulates the uptake of amino acids and other substances into the cell; more-

over, the cell can begin its cycle of division (reproduction) only after it has accumulated certain reserves of these materials.*

It should be taken into consideration that cancer cells consume much more glucose than normal, "healthy", ones. It is known that glucose can be utilized as an energy source either in the cycle of fermentation (where energy is produced without the participation of oxygen, and lactic acid is the final product of glucose metabolism), or in the cycle of respiration (where oxygen is consumed, and the final products are carbon dioxide and water). As far back as the 1930s it was demonstrated in the classical works of the German scientist Otto Warburg that fermentation was increased ten- to thirtyfold in cancer cells. The following question should have naturally arisen immediately after Warburg's discovery: how could such a large amount of glucose enter the cancer cells, which leads to a tremendous (by cell standards) accumulation of lactic acid?

* It is remarkable that the same dependence, though in a modified form, is preserved in an integral organism. The age-related switching on of the reproductive function in girls occurs when the mass of fat (the potential energy material) increases to a certain amount. Therefore, the reproductive function switches on later in female athletes and ballerinas as a result of a reduced amount of fat due to the greater accumulation of muscular tissue.

However, this question was never asked, although a malignant tumour was called a "trap" for nitrogen and glucose. It was as if the role of a "trap" did not require an increase in the transport of glucose into the cell and, consequently, it was unnecessary to ascertain how this increase was ensured.

When elaborating our hypothesis, we proceeded from the necessity of elucidating the reason for the accumulation of lactic acid in malignant cells. As is known, it was first thought that the accumulation of lactic acid in the cancer cell was associated with the reduced utilization of the products of glucose transformation in oxidation processes, which occurred with the consumption of oxygen. This, in turn, caused a shift in the metabolism towards fermentation. However, after 1950, when it was already quite clear that glucose oxidation was not disturbed in cancer cell, the accumulation of lactic acid could be explained only on account of the increased transport of glucose into the malignant cells. We assumed that oncoprotein pp60, which is attached to the inside of the cell membrane, performed the so-called "insulinization of the cell membrane" that ensured an increase in glucose transport into the malignant cell. In light of modern data, it is quite probable that oncoprotein pp60 can perform the function of a receptor that does not

require activation by hormones such as insulin or insulin-like hormones because the receptor enzyme of oncoprotein pp60 (tyrosinekinase) is already in an activated state.

A report was published in 1984 stating that the oncoprotein that is coded by oncogene erb-B and is located on the cell membrane probably performs the function of a receptor. Several examples of this type, where an oncogene codes for the hormone receptor, are currently known. The following question naturally arises: are such changes sufficient to transform a normal cell into a transformed or malignant cell? Before examining how modern data make it possible to answer this question, let's consider again some general principles of endocrinology.

Any process in an organism has a reason for occurring. For example, cells do not divide without receiving a signal from outside. According to our hypothesis, the "insulinization of the cell membrane" ensures the continuous transport of glucose, which, in its turn, we qualify as a signal that stimulates cell division. However, it is known that a signal for cellular division is transmitted by hormones and it should be noted that it is the hormones that exert a growth-stimulating influence which directly or indirectly induces an insulin-like effect, i.e., stimulates the transport of glucose

into the cell. In addition to insulin, other insulin-like hormones are produced in the organism to ensure the transport of glucose into the cell. These hormones are commonly designated as growth factors because they control not only the transport of glucose but also the entire complex of events that leads to the division of cells. Many growth factors are known that influence various cells, e.g., the nerve growth factor, fibroblast growth factor, growth factor secreted by thrombocytes (PDGF), and epidermal growth factor (EGF). Since there are various growth factors in the internal environment of the organism, their effect on one or another type of cell is determined by the presence or absence of receptors for that specific growth factor on the cell's external membrane. When the growth factor binds to its receptor, the latter is activated, i.e., the enzyme that is located in the intracellular part of the receptor is activated, which, in turn, activates the respective intracellular protein. As a result, a cascade of reactions is initiated, inducing, in the final end, the division of the cell.

As is known, malignant cells have a capacity for an infinite number of divisions, which forms the basis for their potential immortality. The researchers who studied the reproduction of sarcoma cells in a so-called cell culture discovered that the sarcomatous growth factor (SGF) accumu-

lated in the cell environment. The addition of SGF to a normal line of connective tissue cells—fibroblasts—imparted the latter with all the features of transformed cells. On these grounds, SGF and other similar factors that were discovered at a later time were designated as transforming growth factors (TGF). Certainly, the transformation of normal cells into malignant ones was temporary because, according to the experimental conditions, the system functioned only as long as TGF was added and without the participation of an oncogene. Under conditions of true transformation, the oncogene could ensure the continuous production of TGF.*

These investigations led to a very important theoretical conclusion on the essential difference between normal and malignant cells. As was emphasized above, the division of a normal cell is induced from the outside by a hormone, or a growth factor. In other words, the endocrine system is organized by at least two elements, viz., the

* At the present time it is believed that cells such as fibroblasts, which can be maintained outside the organism in a cell culture, are already in a precancerous state, and, therefore, only TGF is necessary for their temporary transformation. The oncogene that codes for the secretion of TGF would function continuously in true malignant transformation. Accordingly, the secretion of TGF would be continuous, and the transformed state of the cell would be stably maintained.

cells producing a hormonal signal, and cells perceiving this signal, which ensures self-regulation of the endocrine influences by the feedback mechanism (see Chapter 1). In contrast, as was suggested by M. Sporn and G. Todaro (1980), malignant cells secreted TGF for themselves, i.e., TGF acted on the same cell that produced it. This type of hormonal secretion was designated as autocrine secretion. The autonomy of malignant cells (i.e., their independence from the organism's hormonal signals), which is characteristic of some types of tumours, can be conditioned by the mechanism of autocrine secretion. In accordance, there exists a variant of malignant transformation when the activated oncogene codes for the continuous production of oncoprotein, which possesses the properties of TGF.

It must be noted that autocrine secretion is apparently characteristic of embryonal cells. These cells (just as cancer cells) need hormonal stimulation of glucose transport into the cells. But there are no endocrine glands in the early embryonic period, e.g., the pancreas, which produces insulin, starts to function only during the twelfth week of development of the human fetus. Therefore, embryonic cells must secrete insulin-like hormones that act on these cells by the autocrine mechanism. Indeed, some TGF are released from the embryonic tissues.

The organism, however, switches over to endocrine control with the development of the fetus and appearance of endocrine glands, and the autocrine secretion of hormones terminates (or decreases). The latter is achieved either by blocking (repressing) the effect of the respective "embryonic" genes (oncogenes) that code for the growth factors, or by blocking the oncogenes that produce their receptors. Therefore, it can be assumed that malignant transformation of cells is initiated by the depression (unblocking, or activation) of the genes that code for the secretion of growth factors, or for the synthesis of their receptors. Hence, in essence, these genes are protooncogenes.

Thus, the presence of agents similar to TGF, i.e., factors ensuring increased transport of glucose into malignant cells, could simply be assumed long before they were discovered. The question of what induced the accumulation of lactic acid in tumour cells had to be raised.* Therefore, the significance of our hypothesis took shape owing to the fact that the mechanism by

* In 1980 when we advanced our hypothesis science only knew of the existence of TGF. In spite of this, we wrote, "However, the presence of the Warburg phenomenon in carcinomas indicates that with these types of tumours the transport of glucose is increased. Consequently, the internal insulinizing factor, or the effect determined by it, should exist in all types of malignant tumours, not only in sarcomas."

which oncoproteins induced malignant transformation was correlated with the processes controlled by hormones and growth factors.

It would seem that after the discovery of TGF the assumption of "insulinization of the cell membrane" should have lost its significance because TGF itself could be the agent that, like other growth factors, acts on the receptors of the cell membrane, ensuring an increase in the uptake of glucose (and other nutritious substances) into the cell and the cell's transformation. But this is not the case because there exists not one but several mechanisms that ensure the specific properties of tumour cells and, in particular, increased transport of glucose. One of these methods is the autocrine mechanism itself in which the effect of TGF is realized (Fig. 6). The second mechanism could be called a semi-autocrine one, wherein the oncogene ensures the synthesis of growth factor receptors, although the growth factor itself is secreted by normal cells.* As far as the third mechanism is concerned, it is realized by common (the author stresses, common) growth factors if the gene that codes for the secretion of the growth factor is activated and functions in a con-

* As stated above, the oncoprotein-receptor can be primarily activated and in this case its activation by the growth factor is unnecessary.

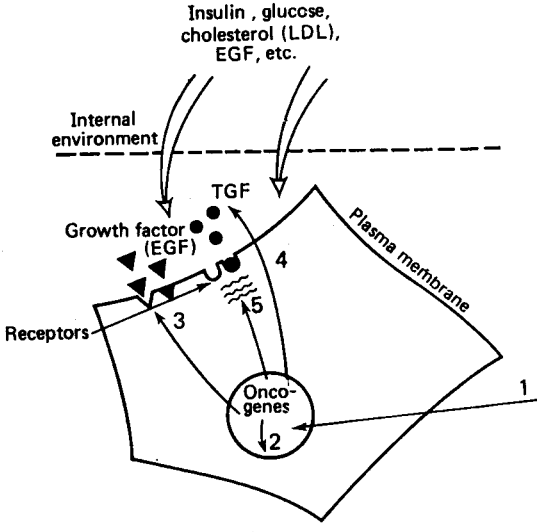

Fig. 6. Autocrine mechanism of cancer cell autonomy: 1—viruses, radiation, chemical carcinogens, free radicals, and other factors that initiate activation of "sleeping" oncogenes by various mechanisms; 2—activation of oncogenes ensuring "immortality" of cells; 3—variant by which the oncogene product (oncoprotein) is localized on the plasma membrane of the cell and performs the role of a receptor for the normal growth factors in the blood (e.g., oncoprotein *erb-B* which acts as a receptor for epidermal growth factor (EGF); 4—variant in which the oncogenes code for the production of transforming growth factors (TGF) that influence the receptors on the cell; hence, reproduction of the cancer cell is realized autonomously, i.e. independently of the factors of the organism; 5—oncogenes that code for the formation of oncoproteins, representing activated phosphokinases that initiate a series of metabolic changes characteristic of the cancer cell.

tinuous mode. This unusual discovery was made by several groups of researchers, but very often, especially in popular scientific literature, it is described as follows. In May 1983, R. Doolittle, a specialist in the chemistry of proteins, who was conducting computer analysis of a large amount of data on the structure of various proteins, fed into the computer data published by other authors on the growth factor released by thrombocytes (PDGF). The computer printout was unexpected: this factor strikingly resembled the previously discovered oncoprotein that was coded for by the monkey sarcoma oncogene (V-SiS). In other words, what is distinctive of one type of viral malignant transformation, and what is in common blood platelets, whose main function is to stop bleeding in wounds, is one and the same, or, to be more precise, almost one and the same. This discovery evoked the impression that the "last mystery of cancer" was soon to be tackled. It was just as amazing that the discovery, in the spirit of scientific and technological progress, was made by a computer. In reality this all started not in 1983 but several years earlier. In any case, in 1980, the Swedish researcher Karl Heldin and coauthors published a paper emphasizing the similarity between the chemical and biological properties of TGF released by human sarcoma cells and those of PDGF. Their similarity lay in the

fact that both these factors, viz., the common thrombocytic and the sarcomatous ones, influence the cell via the same receptors on its external membrane. In 1983, continuing these studies, a scientific group including K. Heldin determined (without the sudden "insight" of the computer) a considerable degree of structural similarity between PDGF and the oncoprotein coded for by the viral oncogene.

It was impossible to immediately assess the unusual significance of these studies. Oncogenes had been discovered only a few years earlier. It had seemed that the term "cancer genes" had stressed new properties of the cell that were obtained by the latter during malignant transformation. But now it turned out that the mysterious oncogene was a common gene coding for the synthesis of a common growth factor. It was still necessary to prove that the growth factor could transform a normal cell into a malignant one if it was secreted by the autocrine mechanism. In 1987, several research groups proved the existence of such a mechanism of malignant transformation. A gene of the epidermal growth factor (EGF) was "inserted" into the genome of a normal line of fibroblasts, and a small section of the gene—a promoter—was "attached", in turn, to the EGF gene. The promoter is a gene that ensures the continuous functioning of the EGF gene and consequently, the contin-

uous secretion of EGF. Fibroblasts with an "inserted" modified gene began to behave like malignant cells.* However, the behaviour of the fibroblasts normalized when antibodies that neutralized EGF on the cell membrane were added to these cells.

Thus, cell oncogenes are not only analogues of viral oncogenes. Any gene that codes for the secretion of a growth factor gains the properties of an oncogene if the impairment of the genome causes continuous activation of this gene and if the receptors for the growth factor are coded for by this gene. It is quite possible that in many cases at least two oncogenes are necessary for malignant transformation of a cell.**

At the same time, as is known, after both the growth factor and TGF act on the receptor (in which the internal part is an enzyme), a series of activating reactions in the system of intracellular proteins is induced. Therefore, it was also possible to as-

* T. Dexter and coauthors had demonstrated earlier (1984) that the cells could either be at rest, or could intensively reproduce or transform, depending on whether or not hemopoietic growth factor was present in the medium, and, moreover, an increase in glucose transport was observed in the given sequence.

** For example, activation of the oncogene c-myc is observed in many cases of malignant transformation and its influence is apparently manifested at the level of the cell nucleus; therefore, another gene must be activated to ensure increased transport of glucose.

sume a variant of malignant transformation wherein the oncoprotein immediately performed the role of an activated intracellular protein. This means the possibility of malignant transformation without the participation of TGF and its receptors (A.G. Golubev and V.M. Dilman, 1983), and even without autocrine secretion of growth factors. Finally, it is known from endocrinology that the receptors of hormones can be activated under certain conditions by antibodies to these receptors, as occurs, for example, when the thyroid gland is overactive (Graves' disease). Therefore, we assumed that an autoimmune mechanism for inducing tumoral growth without the participation of oncogenes, or TGF could, in principle, exist.

Thus, the concept of the oncogene gradually loses its primary meaning and it becomes clearer that malignant transformation of the cell is mainly due to a "breakdown" in the transmission of the hormonal signal. And a "breakdown" in any link of this cascade signal, if the continuous autocrine mechanism begins to function, can induce the transformation of a normal cell into a malignant one.*

* If the term "oncogene" is to be retained, it should be borne in mind that all the genes, which when their functioning is disturbed cause transformation of the cell (and not only viral oncogenes and cell precursors of viral oncogenes), are oncogenes by definition.

In light of all that has been discussed in this chapter, an attempt can be made to elucidate the main difference in the behaviour of a normal cell (with its limited potential number of divisions) and a transformed cell (with its potential immortality). For example, the changes in the cell membrane of a normal cell (the accumulation of cholesterol in it) may cause a loss in the receptor sensitivity to growth factors and a decrease in the synthesis of the receptors. On the other hand, either "constant expression of the receptor systems" (M.V. Blagosklonny, 1985), or constant activation of the oncogenes, whose effect is realized at the postreceptor level (as is characteristic, for example, of the c-myc oncogene) can provide the malignant cell with immortality.

In recent years the optimistic expectations concerning the search for specific methods of treating malignant tumours were associated, first of all, with the discovery of oncogenes. However, as far back as 1981, in the first Russian edition of this book, this author wrote the following: "At the same time the hypothesis of "cell insulinization" transferred the "cancer drama" from the depths of the cell (where the still inaccessible cancer gene resides) to its surface where the membrane receptors are located. This means that if these receptors are blocked by means of antibodies to these receptors, reproduction of the cancer cell

should cease and the cell would become an accessible target for immunological antitumoral protection".

In 1983, G. Carpenter and coauthors wrote that antibodies to the receptor for epidermal growth factor blocked the oncological activity of sarcomatous growth factor. Their publication clearly demonstrated the beginning of a new trend in the search for antitumoral agents.

One more element in the strategy of the cancer cell must be considered when elaborating ways of influencing the tumoral process. Cells, like organisms in a closed population, can experience hunger due to overdensity, or overpopulation. The cell can avoid this by moving to other parts of the organism, i.e., by metastasizing. But it must have a special method for acclimatizing in new tissues. The method is yet unclear but the similarity between embryonal and malignant cells suggests that the fertilized ovum is in the same situation. It must also "acclimatize" in a specified place. It is possible that the elaboration of chorionic gonadotropin, which has an immunodepressive effect, serves this end. It is just amazing that this hormone is produced after only a few divisions following fertilization. Chorionic gonadotropin is also found in the membrane of cancer cells and even in the membrane of some microbes that infect humans suffering from cancer.

It is hard to imagine how information is transmitted from the cancer cells to these microbes, but, most probably, oncofactors are involved.

In the first Russian edition of this book (1981), this author wrote: "Beyond all question one should not neglect the search for biological objects (microorganisms, protozoans, and simply somatic cells) sensitive to oncofactors when elaborating methods for detecting tumours". In 1984, R. Derynck and coauthors identified the chemical structure of one of the oncofactors, viz., alpha-TGF, which contains 50 amino acids. Meanwhile, another goal has been set—the immunological neutralization of chorionic gonadotropin—in an attempt to find a way to counter the strategy of the cancer cell. In particular, it has been demonstrated recently in our laboratory that immunological neutralization of chorionic gonadotropin greatly inhibited the growth of a malignant tumour.

Thus, we have discussed the initial stages of malignant transformation. These stages are associated with the damaging effect of external and internal factors, and it is practically (and theoretically) impossible to avoid this effect, e.g., impairment caused by free radical reactions (Chapter 11). As a result, it becomes clear why medicine will never be able to fully prevent cancer, the more so that this process initially affects

only one cell and, therefore, it is impossible to detect it. But the whole process of malignant transformation and especially the subsequent stages in the development of cancer can, certainly, be prevented.

In essence, this is exactly what usually occurs in reality as the frequency of impairment of the genetic apparatus that can induce the development of cancer is many hundred times greater than the frequency of clinical cancer. This difference is conditioned by the multicomponent character of malignant transformation, which includes several stages at each of which the process can stop, and by the presence of systems in the organism designed to eliminate the transformed (cancer) cell. Let's briefly discuss both phenomena.

Several decades ago, in an experiment on the origination of carcinoma cutaneum, this process was determined to occur in two stages. It is quite obvious today that the number of stages can be much greater. We'll limit ourselves to considering three clearly outlined stages.

When a small dose of a carcinogen is applied to the skin, it often appears that there is no pathology, i.e., tumours do not grow and no changes are found in microscopic studies of the skin cells. But, if certain substances that do not in themselves induce carcinoma are applied to the skin after the carcinogen, tumours are discov-

ered after some time. The substance used in the first experiments was croton oil, which, as is known, causes a strong inflammatory reaction. Later, about 25 substances were extracted from croton oil (so-called phorbol diethers) that act just like the oil proper though the inflammatory effect is not pronounced. Proceeding from these experiments, two stages in malignant transformation were differentiated, viz., the stage of initiation, which is conditioned by the impairing effect of the carcinogen on the genetic apparatus of the cell, and the stage of promotion (advancement), which is conditioned by commonly noncarcinogenic substances that have been called promoters.

Numerous observations confirm that these stages exist not only under experimental conditions but also in similar real situations. For example, in the forties and fifties of this century X-rays were often used in medicine for treating inflammatory processes (frequently, chronic inflammation of the tonsils) and for irradiation of an enlarged thymus (at that time it was a gland of unknown significance for the organism, see Chapter 9). In both cases, the thyroid gland was exposed to radiation. As a result, the incidence of struma maligna increased sharply in irradiated humans. The direct impairing effect of the X-rays was very brief, yet initiation (origination) of the malignant process is related precisely to this

period of irradiation. From these observations it follows that the cells can be in a precancerous condition for many years before a tumour commences to grow under the influence of some other factor (promoter).

Many similar authentic cases are known today in which the time interval between the initiation of a malignant process and its clinical identification is determined quite accurately. The contemporary understanding is that the latent period between carcinogenic initiation and clinical identification of the tumoral process is not less than 10 years on the average. However, this conclusion is obviously incorrect when cancer occurs in children (in rare cases even during their intrauterine development), as well as in young adults. The reasons for this contradiction will be discussed below.

A tumour begins to form in the organism when the initially transformed cell becomes a truly malignant one (i.e., the cell has passed the stages of initiation and promotion). With an increase in the number of tumour cells (i.e., as their origin is less and less directly related to the initial cancer cell), the cells themselves become more malignant, apparently, due to activation of additional oncogenes. This third stage in the development of cancer is designated as the stage of progression.

Bearing all this in mind, modern oncology interprets the reasons for the age-related

increase in the incidence of cancer as follows. As is known, the incidence of cancer increases almost 100-fold between the ages of 20 and 65. It is usually thought that this increase is conditioned mainly by increased exposure to various chemical carcinogens because it is known that the greater the dose of carcinogen received by the organism in a certain period of time, the greater the probability of cancer. The carcinogens may not only cause damage to the genetic apparatus that induces cancer, they may also stimulate the division of cells, which is necessary for the stage of promotion. As a result, it is frequently concluded that it is sufficient to lower the concentration of carcinogens in the environment (or to eliminate the carcinogens completely) in order to decrease the incidence of tumours observed in humans by more than half. However, the appealing obviousness of this approach greatly simplifies the problem.

Let's consider the results of a modern experimental observation made by Robert Good and coworkers. Through selection, cancer-susceptible strains of animals (in particular, cancer strains of mice) were derived. Carcinoma of the mammary gland arises in 71% of the five-month old mice in one of these strains. At the same time, when the food ration of the animals was artificially reduced by 37% as compared to the ration ingested when the mice had

free access, no mice of this age developed a tumour.

The latter observation is not unique. It has been increasingly observed since the 1940s, indicating that not only the duration of action or concentration of the carcinogenic agent, but also the condition of the organism determine the probability of developing cancer.

But perhaps the data obtained in the experiment has nothing in common with the development of cancer in humans? Actually, numerous statistical observations confirm that obesity increases the probability of all kinds of tumours in humans. Hence, if the development of cancer depends on the time of exposure to the carcinogenic factors, then time passes faster in obese humans. And in general, when it is stated that the carcinogenic effect is proportional to the duration of the exposure to the carcinogenic agent in a human, it must be remembered that not only does the time factor increase the carcinogenic dose received by the organism, but the latter itself changes over time in the process of aging. In particular, age-related obesity is a regular occurrence with increasing age.

In the experiment described, how can the retarded onset of the "cancerous age" be explained when restricting the caloric value of the diet, and, conversely, how is the "carcinogenic time" accelerated when there

is a surplus in body mass? It seems most logical to look for an explanation among the regular patterns that determine the age-related development of atherosclerosis and metabolic immunodepression, or, more generally, among the laws governing the growth and development of the organism.

The condition of the organism can influence all stages of the development of cancer, i.e., initiation, promotion, and progression. It significantly determines whether cancer in general develops as a disease, and influences the course of the tumorous process if it does develop.

Already at the stage of initiation the organism has some protective mechanisms. Ignoring the various ways of rendering carcinogens in an organism harmless, one need only be reminded of the existence of systems of recovery (repair) of the damaged DNA structure, i.e., repair of the structure of the genes. It is assumed that this system of repairing DNA appeared at the dawn of the origin of life when the main role in inflicting damage was performed by factors in sunlight, including ultra-violet rays whose effect on the cells intensified due to the absence of oxygen in the atmosphere (see Chapter 11). The data on a series of genetic diseases where there are inborn disturbances in the mechanism of DNA repair indicate that DNA repair systems also protect the genes at the stage of can-

cer initiation. In these diseases (xeroderma pigmentosum, familial polyposis, Fanconi's anemia, etc.) the incidence of cancer is dozens and hundreds of times greater as compared to the usual figure.

However, after the stage of initiation the condition of the organism influences the development of cancer. This follows from the presence of a long period during which the stage of promotion that follows transforming damage of the cell may not be realized. As stated above, certain substances, e.g., phorbol compounds, which have no relation to the organism, are promoters of the tumorous process. But recently receptors have been discovered on the membranes of cells through which phorbol compounds act. It follows that the organism contains similar physiological substances for which the stated receptors are naturally intended. The fact that the latent period in the development of cancer can extend to dozens of years indicates that the promoter effect intensifies with age. This means that this can be counteracted under certain conditions. In particular, though the effect of promotion is not reduced to only intensification of cell division, it always requires a certain number of cell divisions, and this phenomenon is greatly controlled by the factors of the medium washing over the cell.

The following experiment demonstrates

this. When an insufficient quantity of iodine, which is an essential component of thyroid hormone, is taken in by the organism with food and water, the concentration of this hormone in the blood decreases. This decrease, which weakens the mechanism of negative feedback, increases the activity of the part of the hypothalamic-pituitary system that stimulates the function of the thyroid gland. The cells of the thyroid gland divide intensively as a result of increased stimulation, which increases the "working area" of the organ. This compensatory increase is directed to meet the deficiency in thyroid hormone. But, as the amount of iodine is still insufficient to produce the hormone (its content in the food and water is reduced experimentally), equilibrium is not restored and the thyroid gland is in a condition of permanently increased stimulation. Benign tumours form in this "overstimulated" gland, and even malignant ones if excessive stimulation continues long enough. However, if the animals are injected with thyroid hormone at the onset of benign tumour formation, equilibrium is restored in the system and the development of cancer is prevented.

This example demonstrates that one of the conditions that contributes to the onset of cancer is an increase in the rate of cell division. This condition is so important that cells that lose the capacity for division

in an adult organism do not in general transform into cancer cells.

Finally, the immune system with its various subsystems provides powerful antitumorigenic protection. F. Bernett, the outstanding Australian immunologist, developed the concept of the existence of "immunological surveillance", which protects the organism against "foreign" cells. This is a well-known phenomenon. It is observed in organ transplantation, e.g., of the heart or kidneys, and when treating certain diseases. But, certainly, this situation is not encountered under natural conditions, except for the period of pregnancy when immunological supervision of the maternal organism may cause rejection of the fetus because, like a transplant, it combines "own" (maternal) and "foreign" (paternal) antigens.

Bernett assumed that immunological surveillance is directed against tumorigenic cells under natural conditions. Therefore, the incidence of cancer increases 100 to 300 times in children with a genetic (inborn) deficiency of transplantation (cell) immunity, or in cases when some substances exert a toxigenic effect on immunity. It can be assumed that the relatively high frequency of malignant processes in children under the age of 15 is most often conditioned by certain defects in the immune system, in particular, most likely by a decrease in

antiviral immunity. The frequency of malignant diseases decreases after this age and begins to increase only at the age of 30 when an accumulation of damage caused not only by viruses but also by other factors of carcinogenesis can be observed.

To perform its protective function, the system of immunological surveillance must familiarize itself first with the tumorigenic cells that are "foreign" to the organism. In its turn, the degree of foreignness of the transformed cells can be quite diverse. For example, if the embryonal mechanism of oncogene activity has been unblocked under the influence of a chemical carcinogen and true mutations have developed, a mutational increment to the foreignness ("mutational noise") may be created. From this point of view it is possible to explain why in an experiment each tumour that has been induced by one and the same chemical carcinogen is immunologically different, while all viral tumours are homogeneous.

In the organism, a so-called natural subsystem of immune protection also functions, which does not need preliminary "training" to begin an antitumorigenic attack.

The conclusion can be drawn that no matter what the factor is that induces malignant transformation of the cell, the probability of the onset of cancer is higher the greater the number of cells dividing in the tissue, the less the activity of cellular im-

munity (transplantation immunity) and of the macrophages (cells playing an important role in the "natural" system of antitumorigenic immunity), and the lower the activity of the systems repairing damage in the DNA structure.

As demonstrated above by the example of inborn deficiency of immunity and DNA repair each of these three conditions can independently influence the development of the tumorigenic process. At the same time, this author advanced the suggestion that conditions that contribute to the development of cancer are also created by the hormonal-metabolic shifts characteristic of normal aging (Chapter 11). The idea of cancrophilia ("love for cancer") as a normal disease was formulated on this basis. Indeed, metabolic immunodepression, which arises regularly in the process of normal aging, is one of the components of cancrophilia (Chapter 9). At the same time, reduced immunity is enough to increase the probability of the onset of cancer.

The assessment of the role of hormonal-metabolic shifts in increasing the number of multiplying cells is yet far from complete. According to some calculations, about 20% of tumours in humans develop in so-called endocrine-dependent organs. It is possible in these cases to record the association between the age-related increase in cell multiplication and the development of cancer

(examples concerning the reproductive organs are given in Chapter 5). In addition, elevation in the lipid concentration in the blood (cholesterol and fats) contributes to the multiplication of cells, which is well-known in relation to the cells of the vascular wall (see Chapter 9). It has also been shown that "diabetic blood" with an increased concentration of lipids stimulates the multiplication of cells in the mucous membrane of the intestine. It should be noted that the concentration of serous growth factors in the blood (somatomedins and the growth factor PDGF, which is released by thrombocytes) can increase in certain disturbances in fat and carbohydrate metabolism.*

The influence of age-related metabolic shifts on the intensity of cell division during the impairment of cells (or tissues), which is more in conformity with conditions leading to the development of cancer, has not been studied at all. For example, cancer of the lungs develops in approximately one

* It is often stated that the number of dividing cells in old age decreases despite the presence of metabolic shifts and, therefore, the "division factor" should not be considered a component of age cancrophilia. But if it is considered that the latent period of cancer development is quite long (see above), then the metabolic shifts and the intensity of cell division should be compared not in old age, but between the ages of 35 and 45 when, apparently, the incidence of cancer is at a maximum.

out of ten smokers. But, the probability of cancer increases sevenfold in smokers with an increased concentration of cholesterol as compared to those with a decreased concentration in the blood.

Finally, it is possible that the metabolic shifts can suppress the DNA repair system, though this problem is still insufficiently studied.

Nevertheless, without elucidating all the theoretical aspects of cancrophilia, we can suggest certain measures that prevent the development of cancer. This author suggested new approaches to the prophylaxis of cancer on the basis of concepts about cancrophilia. For example, the use of phenformin (a preparation that decreases the incidence of disturbances in fat and carbohydrate metabolism characteristic of aging, see Chapter 16) led to a considerable decrease in the incidence of cancer in animals induced by either chemical carcinogens or viruses.*

* As far back as 1967 the author of this book assumed that preparations that improve the metabolism of carbohydrates and correspondingly decrease the content of cholesterol in the blood can be used for the prophylaxis of cancer (*Lancet*, 1971, 1, p. 1211). Epidemiological studies have currently determined a direct correlation between the content of cholesterol in the diet and the incidence of cancer, especially cancer of the large intestine, prostate, uterus, and mammary gland. However, the role of metabolic immunodepression has still not been considered in this correlation (Chapter 9).

The concept of cancrophilia explains in many respects numerous data (experimental and clinical) on the increase in the incidence of cancer in overnutrition and on the opposite effect, given rational limitation of the caloric value of the diet, i.e., optimal nutrition. It follows also that cancrophilia occurs not only as a result of age-related disturbances in metabolism but also due to the influence of unfavourable external effects, e.g., overnutrition, or an increased content of cholesterol, fats, etc., in the diet.

Thus, it is obvious that measures directed towards reducing the quantity of carcinogens entering the organism play an essential role in the prophylaxis of cancer. This is most important for the prophylaxis of cancer of specific organs, first and foremost, cancer of the lungs and, probably, of the stomach. But it must be taken into consideration that in reality it is impossible to eliminate all the ecological carcinogenic influences, especially when bearing in mind the carcinogenic effect of viruses, or ultraviolet radiation. Attention also should be given to the fact that the incidence of cancer is not greater than 30 % in all industrially developed countries, i.e., in countries with a sufficiently long lifespan. The living conditions (and, correspondingly, the type of carcinogenic hazard), influence the type of cancer that develops rather than the general rate of incidence. For example, as

the incidence of cancer of the stomach decreases in some countries owing to changes in the diet, the incidence of cancer of the large intestine increases. Therefore, prophylactic measures undertaken by the individual, e.g., normalization of metabolism (individual anticarcinogenesis), are necessary whatever the specific features of the external environment.

Certainly, cancrophilia, or the sum total of metabolic conditions that contribute to the onset of cancer, arises not only during normal aging, or in cases of poor nutrition, but also under the influence of many external and internal factors. Let's discuss some of them.

There is no doubt today that chronic stress contributes to the onset of cancer (or aggravates it). At the same time, metabolic shifts that are characteristic of stress (Chapter 2) are related to cancrophilia. In addition, it has been shown that the major stress hormone, cortisol, may induce activation of the viral oncogene, i.e., it can exert an effect during the stage of cancer initiation. Negative emotions, hyperadaptosis (Chapter 4), and mental depression act in this respect as chronic stress.

Similarly, all the factors (or states) that disturb the sensitivity of the hypothalamus to regulatory signals or enhance the utilization of fat as a fuel contribute to the onset of cancer. Thus, excessive illumination

(in addition to the fact that the ultra-violet part of the spectrum induces mutations) elevates the sensitivity threshold of the hypothalamus to regulatory signals. Hence, constant illumination in an experiment intensifies the development of tumours.

Enhanced mobilization of fat, which is induced by nicotine, or excess intake of caffeine from tea, or coffee, also enhances the development of cancer under experimental conditions. Apparently, many carcinogenic chemicals contribute to the development of tumours not only as a result of genetic impairment, but also owing to the effect of disturbances in metabolism. This fact allows this author to introduce the concept of *carcinogenic aging*.

Finally, the tumour itself causes disturbances in the organism that are similar to those in common cancrophilia.

Conversely, everything that normalizes the activity of the hypothalamus and reduces the utilization of fat as a fuel serves the purposes of cancer prophylaxis. As stated above, this is how a rational diet, increased physical activity, and the antidiabetic preparation phenformin render their favourable influence.

When studying diseases, researchers strive to determine the cause of onset, or etiology, and the mechanism of its development, pathogenesis. Proceeding from the fact that cancer can be induced by various

factors (viruses, carcinogenic chemicals, physical factors, and hormones), N. N. Petrov, an outstanding Soviet oncologist, called cancer a polyetiological (multi-causative) disease. But if one takes into consideration the fact that all these causes initiate the same changes in the activity of the cell, one can state that cancer is a polyetiological and monopathogenetic disease. This means that all the causes "actuate" the same mechanism of malignant transformation of the cell.

Monopathogenicity, i.e., the uniformity of the final mechanism that transforms a normal cell into a cancerous one, does not mean that in all cases this transformation is accomplished by the same method and the same genes. On the contrary, in the process of embryonal development, various oncogenes, or, in the given context, various genes controlling the development and differentiation of tissues, are switched on and off. Consequently, the unblocking of these various genes and their combinations can cause malignant transformation of the cells by different methods. But, in the final end, the properties of the cancerous cells are similar, e.g., their capacity to produce an increased amount of lactic acid. This reflects the monopathogenicity of malignant transformation of the cell.

In addition to these factors, there also exist conditions that might contribute to,

or, on the contrary, prevent the onset of cancer. These conditions can arise episodically, or exert a continuous influence. Thus, cancrophilia, "love for cancer", like love in general, can be passing (if cancrophilia arises under the influence of stress, or overnutrition), or constant (when a normal or accelerated aging process forms the basis of cancrophilia). Probabilistic factors that "accidentally" cause initiation of the malignant process in humans, as well as regular factors of cancrophilia that increase with age the probability of the development of a malignant tumour from an initially single transformed cell, are important in the aforementioned case in the onset of cancer, and especially in the age-related increase in its incidence.

At the same time, R. Peto, a well-known British oncologist-theoretician, when examining the reasons for the age-related increase in the incidence of cancer, contrasts two hypotheses that he considers mutually exclusive. One of them is the hypothesis concerning the key role of carcinogens, of which he considers himself a proponent; the second one is the hypothesis concerning the role of the hormonal, metabolic and immunological mechanisms, which according to R. Peto and coauthors (1975) has been mainly elaborated in its modern form

by M. Burnet* and the author of these biological essays.

In reality, neither an alternative nor the requirement of choosing between these hypotheses exists: in the first case, an external cause or causes initiating a malignant process are dealt with; and in the second case conditions contributing to the onset of this process are addressed. The prior case also deals with a random event (though with a certain probability of realization in time), while the latter concerns regular phenomena that develop with age or under the influence of other causes that disturb the metabolism. Therefore, it is incorrect to contrast the contribution of each of these phenomena to carcinogenesis (R. Peto), or to combine them, because the reasons for the development of cancer and the conditions for its development are different phenomena. It is precisely the hormonal and metabolic shifts that are characteristic of cancrophilia and contribute greatly to the increase in the incidence of cancer.

All this makes it possible to state that one of the most realistic methods for delay-

* According to Burnet, an accumulation of mutations in immune cells and exhaustion of the immune system, conditioned by the genetically programmed limit in the number of cell divisions in the thymus, form the basis for the mechanism of the age-related decrease in the effectiveness of immunological surveillance.

ing the age-related increase in the incidence of cancer, without even fully comprehending its nature, is the normalization of the metabolic processes and, ideally, homeostasis as a whole. However, great difficulties lie along this path. Disturbances of homeostasis regularly emerge in the course of aging even (though at different rates) under the most favourable conditions in the external environment, and damages at the level of the cells and tissues accumulate conditioned by the effect of external and internal factors. This makes aging the most universal disease not only because it is natural for everyone, but also because the signs of all normal diseases are inherent in aging.

Chapter 11

Aging: The Most Universal Disease. The Role of Random and Regular Processes

> Nobody dies of old age: humans die in old age of diseases. Old age itself is a disease, or, to be more precise, the sum and combination of disturbances in the homeostasis and random failures.

Though gerontologists are not unanimous in assessing the main subject of their research, the majority of them undoubtedly do not consider aging to be a disease. Their major argument is that aging is natural for everyone. Is it possible, they argue, to consider the entire human genus as a category of "patients" beginning with a certain age? From their point of view, it is conditionally possible to consider premature aging as a disease, because there they find a disturbance in the normal process of aging.

However, in light of what has been stated in this book, aging is a disease, and a disease not only in essence, but also according to a specific definition of the concept "disease". Let us consider the following example. The rate of utilization of glucose by the peripheral tissues, mainly by muscular tissue, regularly decreases in the course of aging. This is easy to observe. Human subjects of different age groups are given a certain

amount of glucose dissolved in water; the edible glucose is absorbed after some time and its concentration in the blood increases. The higher the age of the subject, the higher the concentration of glucose in the blood. In essence, if the results of the test are interpreted in a strictly scientific manner, this is a symptom of diabetes mellitus in the precise sense of the term, because there is retarded utilization of glucose as a fuel.

Certainly, the common age-related decrease in utilizing glucose is not diabetes mellitus in the medical sense. But in the exact sense it is a disease, because any stable disturbance in the homeostasis can be called a disease.* The longer duration of the elevated blood sugar level (as compared to the norm) after the intake of glucose is in this case, as in diabetes mellitus, a symptom of a disturbance in the homeostasis.

But homeostatic disturbances characteristic of aging are not only restricted to this example. It is not only the rate of utilizing glucose that decreases in the course of aging. The release of insulin also increases in response to the glucose, which lies at the basis of the age-related increase in the organism's

* According to a more complete definition, any stable disturbance in the homeostasis can be called a disease, because any pathophysiological process that increases the probability of death is a disease.

fat content, i.e., age-related obesity (Chapter 7). In turn, these shifts increase the concentration of triglycerides and cholesterol in the blood (to be more precise, very low-density and low-density lipoproteins, which transport triglycerides and cholesterol in the blood). Table 4 presents data characterizing these age-related changes in healthy men.

With increasing age, the blood concentration of gonadotropins (the hormonal regulators of reproduction) increases, which, in turn, is conditioned by hypothalamic changes and, in particular, by a decrease in the concentration of catecholamine neuromediators in the hypothalamus, e.g., dopamine and norepinephrine. On the whole, regular shifts occur in the energy, adaptational, and reproductive homeostats with age; accordingly, three normal diseases, viz., obesity, hyperadaptosis, and the climacteric, set in with a varying degree of pronouncement. Nevertheless, these are not all the pathologic processes that are organically merged with aging. Another example follows.

Often, in old age, a worsening in one's mood is noticed. This sometimes acquires the features of mental depression. We are used to thinking that a bad mood is a consequence of tiredness and physical discomfort, or, in some cases, the result of troubles that accumulated during one's life. But things are not so simple.

Table 4. Age-Related Changes in Metabolic Indices of Healthy Men

Parameters	Age groups (years)				
	4-19	20-29	30-39	40-49	50-59
Fasting sugar level in blood, mmol/l	4.2±0.1	4.4±0.1	4.7±0.1	4.7±0.2	4.7±0.2
1 hour after glucose intake	4.6±0.2	5.5±0.2	6.5±0.6	7.3±0.5	7.8±0.4
2 hours after glucose intake	—	4.7±0.3	5.3±0.4	5.8±0.5	6.5±0.6
Insulin level in blood, mmol/l:					
on empty stomach	136±17.2	165±26.5	136±20.8	179±43.0	265±93.3
1 hour after glucose intake	265±20.8	416±110.5	452±78.9	703±143.5	631±114.8
2 hours after glucose intake	—	308±92.5	459±121.9	847±57.4	631±81.4
Deviation from ideal body mass, %	−3.4±6.3	−8.3±2.5	+1.2±3.0	+3.3±3.1	+2.3±2.4
Cholesterol, mmol/l	4.9±0.3	4.4±0.9	5.3±0.2	5.6±0.2	5.9±0.3
Triglycerides, mmol/l	1.06±0.1	1.14±0.1	1.36±0.1	1.51±0.1	1.71±0.04

Sometimes young, healthy people fall ill with mental depression, frequently without a serious external reason. It turns out that the content of neuromediators, viz., serotonin and norepinephrine, is reduced owing to metabolic disturbances in the hypothalamus. And what is more, temporary apathy can also be a consequence of mental depression, because an increased amount of neuromediators is used in the process of antistress protection by the hypothalamus.

But the age-related decrease in the concentration of these mediators in the hypothalamus is directly linked with the climacteric. If it is taken into consideration that the climacteric regularly develops as an element of aging, then the age-related loss of good spirits is a result of the developmental program of the organism, i.e., one more "planned" normal disease.

There is nothing unexpected in this because the climacteric and mental depression are two consequences of the law of deviation from homeostasis, and in both cases an elevation in the hypothalamic sensitivity threshold occurs. The possibility of diagnosing mental depression by the decrease in hypothalamic sensitivity to the inhibiting effect of the "adrenal stress hormones" (e.g., dexamethasone) is based on this phenomenon. Recall that a test with dexamethasone is used to detect hyperadap-

tosis (Chapter 4). There is nothing uncommon in this either, because diseases that are linked with age are characterized by interconnection and mutual penetration of symptoms.

The changes that cause the major diseases of aging seem to be composed of two parts. On the one hand, they are conditioned by hypothalamic shifts, which is characteristic of the climacteric, hyperadaptosis, mental depression, and, partially, of hypertensive disease, as well as age-related obesity. On the other hand, they are induced by disturbances in the metabolism, as in the case of obesity, type II diabetes mellitus, metabolic immunodepression (partially, in auto-immune diseases), atherosclerosis, and cancrophilia. The very development of age-related metabolic disturbances is due to regular hypothalamic shifts (as is clearly manifested in disturbances in appetite regulation which results in obesity).

Thus, there are not just three diseases that characterize changes in the three basic homeostats and are the major reasons for death in modern humans. In essence, a complex of 10 diseases must be considered as the major human diseases. Indeed, this complex combines two methods for realizing the law of deviation from homeostasis, i.e., the method inherent to the period of pregnancy forms the metabolic component of diseases, and the method that enhances the

capacity of the basic homeostatic systems in postembryonal growth and development creates the "hypothalamic" part of regular diseases and aging, imparting aging per se with all the properties of these diseases.

Indeed, it is sometimes possible to observe all the ten major diseases simultaneously in one subject. This complex is frequently displayed in some types of cancer, making it necessary to ask once and again whether these ten diseases really exist separately, or they are ten symptoms of one integral disease, i.e., aging.

When attempting to answer this question, it should be borne in mind that aging itself is a disease, or, to be more precise, a sum of homeostatic diseases. Hence, it is not a disturbance in the constancy of the internal environment, but precise realization of the law of deviation from homeostasis that determines the diseases of aging. If these diseases do not originate in a certain period of life, this points to deviation from the norm.

Diseases that are linked with aging begin to unfold immediately after the organism has completed its development because they constitute a continuation of development (Chapter 3). To be more precise, after development has ceased (which can be indirectly judged by the termination of linear growth and the preparation of the reproductive system for reproducing one's self),

the "motive forces" that determine the fulfilment of the law of deviation of homeostasis for the development of the organism continue to act as they did during development. Let's consider a most typical example.

A certain amount of gonadotropins is produced between the ages of 20 to 25, which causes the reproductive system of a female to mature. The organism reaches its optimal development at about this age. Let's assign a unit value of one to the quantity of these regulatory hormones during this period. Then, it follows that the content of gonadotropins in the urine by the age of 45 to 50 is five times higher. It is clear that there is no physiological necessity for this increase. The increase in gonadotropin production is a result of the continued functioning of the mechanism that earlier ensured sexual maturation. This mechanism is the elevation in the hypothalamic sensitivity threshold to the regulatory effect of the female sex hormones (estrogens). Correspondingly, an increase in the production of gonadotropins after the age of 25 years is also a result of the elevation in the hypothalamic sensitivity threshold to female sex hormones (estrogens).

Recall that it is necessary to preserve quantitative indices of the interaction between the elements to realize self-regulation in any system. When the interaction between the elements in systems regulated by

the feedback mechanism is disturbed, then the activity of the system itself is disturbed.

The termination of the reproductive capacity, i.e., the climacteric, is a result of this disturbance (Chapter 5). By the mechanism of its origination, the climacteric is simultaneously a clear display of the aging process (because it always appears with inevitable regularity) and a disease (because it is caused by a stable disturbance in the homeostasis). In other words, the climacteric is a normal disease of normal aging.

In considering this example, it is revealed that there is no special program conditioning the origination of aging. Beginning with a certain age, the program of development of the organism transforms into a mechanism of aging and age-related diseases. Aging and specific (i.e., normal) diseases of aging are in this sense a by-product of the realization of the developmental program.

In light of all that stated above, it would seem that the convincing argument of all traditional gerontologists, viz., that everything that occurs in everyone is the norm of aging and, therefore, should not be called a disease, can be interpreted in quite an opposite manner, viz., that what occurs in everyone is dangerous for everyone. Those who consider aging the norm are tacitly ignoring the fact that aging progressively

aggravates the risk of death from normal diseases at the basis of which lies a disturbance in homeostasis. Thus, the majority of people are basically healthy between the ages of 25 and 55 and they feel well. But the death rate from atherosclerosis of the cardiac vessels in this age span increases approximately 100-fold.

When speaking of earlier manifestations of symptoms of aging, let's note some specific features that relate to the higher nervous activity. Currently, an essential correction has been made concerning the widespread view that there is a significant increase in the death of nerve cells with age. The accelerated death of nerve cells occurs mainly in the parts of the brain where the blood circulation is disturbed as a result of atherosclerosis. In other words, these changes in the brain develop secondary to the pathologic disturbances. Therefore, a weakening in mental faculties is not an obligatory manifestation of aging. Many examples taken from the history of science, fine arts, philosophy, and politics reveal that the preservation of high intellect in old age does occur.

Some psychologists think that there is no age-related decrease in the ability to solve problems that characterize the state of the intellect, but that the emotional tension inherent to aging causes an increase in the time spent for their solution.

It is noteworthy that the considerable prolongation in the average lifespan that has been currently attained is reflected by the state of the body, leading to modern diseases of aging. At the same time there is hardly any doubt that the human faculty for reasoning was just as developed two millenia ago as it is today. Heraclitus, Hippocrates, Archimedes, Pythagoras, Euclid, Socrates, Plutarch, Euripides, Aristotle, and many other ancient thinkers would adorn the modern epoch.

Certainly, the major human diseases are not only linked to the mechanism of aging. The same diseases can arise randomly even in young people as a result of failures in the complex systems of the organism. And what is more, many external factors may induce any of the ten major diseases. Therefore, the picture of aging in any individual person implies its own specific features that depend on the internal factors of aging and genetic properties of the individual as well as on the influence of numerous external factors, which each organism is inevitably and frequently subjected to.

These problems shall be discussed in a special part of the book that deals with various models of the emergence of diseases (Chapter 12). Here, the aging model that has been suggested by this author will be compared with other hypotheses and theories.

First, let's note the following: the manifestations of aging in higher animals, including humans, are so diverse that the idea that there is one particular or key reason of age-related changes is usually intuitively rejected. Indeed, aging affects every cell, tissue, organ, and system. Probably, only one definition of this phenomenon that is based on the correlation of aging and death rate has become widespread in scientific literature owing to the complex character of the aging process.

In 1925, B. Gompertz, a British researcher, found that after the age of 35 the specific death rate increases exponentially with age so that the likelihood of death doubles about once every 8 years (Fig. 7). Correspondingly, aging of the organism is determined to be a natural process that increases the probability of death in parallel with an increase in chronological age.

Proceeding from this definition alone, many biologists try to understand the reasons for aging and death, which is hardly correct. Gompertz's mathematical correlations reflect the changes occurring in a totality of living organisms, i.e., in a population. They do not reflect the concrete events that lie at the basis of the aging mechanism per se and its manifestations. Therefore, no information can be obtained on the essence of aging itself by analyzing statistical curves of mortality (or survival).

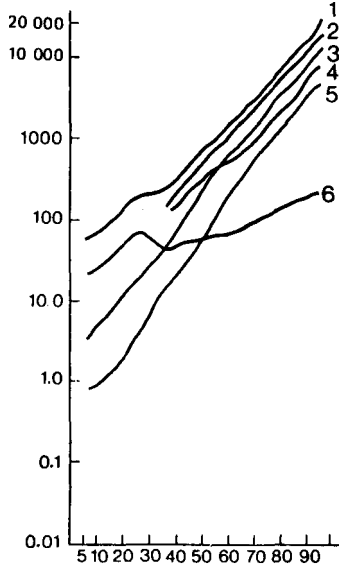

Fig. 7. Age dynamics of mortality from major diseases: x-axis, age (in years); y-axis, deaths per 100 000 subjects (by R. Kohn for 1955); 1—total mortality; 2—all tumours; 3—cardio-vascular-renal diseases; 4—atherosclerosis; 5—vascular diseases of the brain; 6—diabetes mellitus.

However, the lack of a sufficiently elaborated definition of the essence of aging did not present an obstacle to the advancement of various hypotheses on the origin of this phenomenon.

The concepts on aging were modified as human knowledge about living nature im-

proved and changed. The development of the natural sciences rendered the greatest influence on the formation of views concerning these particularly biological and human problems.

When the great achievements in physics, in particular, in mechanics, uncovered before astonished humankind the amazing order in nature, where everything seemed to be predetermined, or determined, living nature, including human beings, began to seem similar to common, though complex, machines. In this connection, aging was considered as a natural result of disorder due to wear or fatigue of the "parts" in the complex machine of the human body, just as most perfect metals break down and wear out in modern constructions. V. N. Nikitin states (1982) that the theory of "wear" was suggested by E. Maupas in 1888. Nikitin's theory on the self-attenuation of synthetic processes in the genome and in the protein-synthesizing apparatus of the cell can be related, in principle, to the same group of phenomena, because it does not establish the reasons for these age-related changes.

Later, knowledge was gained on the energy of nature, which supplemented the picture of the world. It became clear why "nothing lasts forever": the laws of thermodynamics with the inexorable consistency of increasing entropy impose bans limiting

in time the existence of any system. M. Rubner (1908) suggested the "energy" theory of aging, wherein it was determined that the product of the expenditure of energy (index of metabolism in kcal/g/day) and the maximal lifespan (in years) was a constant for higher organisms. In accordance with this rule, an explanation was offered for why small animals with a correspondingly greater ratio of the surface area to the body mass and therefore suffering greater heat losses died faster.

Meanwhile, living systems of organisms (like open systems) have the ability to temporarily counteract the ban set by the thermodynamic laws of nature owing to the metabolism and the supply of energy from the external environment (E. Bauer, *Theoretical Biology*, Budapest, 1982; E. Schrodinger, *What Is Life? From the Point of View of a Physicist*, 2nd ed., Leningrad, 1972; A. I. Zotin, In: *Biology of Aging*, Leningrad, 1982). But if these laws can be counteracted at least within the species lifespan of one individual, then why is its existence finite? Obviously, there are some specific reasons that gradually disturb the properties that distinguish living organisms from all other natural phenomena.

When the laws of genetics were revealed, and the structural fundamentals of the genes of higher organisms, which consist of complex molecules of deoxyribonucleic

acids (DNA), were elucidated, many scientists began to think that damage to the structure of DNA (so-called mutations) accumulates and then is gradually reproduced in the process of cell division, or in the activity of the cells. This leads to aging. In this case the functioning of the organism becomes disorganized, which corresponds to physiologic aging. The mutational theories include: the hypothesis of L. Szilard (1959), which relates aging to irradiation from sources in space; the immunological theory (Burnet, 1971; Walford, 1969); in part, the theory of the "catastrophic accumulation of errors" in protein synthesis (Orgel, 1963); and some other theories. An organism either becomes deranged owing to the accumulation of errors in its operation, or it becomes vulnerable to the effect of numerous external factors, ranging from bacteria and viruses to emotional stress. Its death is then determined by the sum of random causes that always exist during interaction of the organism with its habitat.*

Mutations and the accumulation of errors may really be significant in the formation of many phenomena of aging. They also play a great role in the evolution of living

* Similar considerations on the role of external factors in the causes of death are discussed in metabolic theories (B. Strehler, *Time, Cells, Aging*, 1964; H. Selye, *The Stress Theory of Aging*, 1976).

nature. Therefore, the theories of aging, based on consideration of these processes, are currently being seriously studied. In particular, scientists are interested to find out why organisms that have the ability to repair DNA, whose structure has been damaged, are less efficient in accomplishing this with the passage of time than in the prime of life.

"Mutational" theories of aging to a certain extent coincide with modern views on the physical nature of the world, where much is subordinated to statistical regularities, while the strict order of deterministic phenomena that is characteristic of classical mechanics seems to be too rough a model of what exists in living nature.*

The "programmed" type of aging theories represent a special group. The one best known today is the theory based on the so-called Hayflick limit, which establishes the genetically determined number of possible cell divisions for each species of organisms. (There are serious objections to this theory. First of all, doubts are expressed in regard to adequacy of the conditions for cell division inside the organism and outside of it,

* The concept of gene regulation introduced by V. V. Frolkis (1970, 1975) relates to the probabilistic theories because the primary changes that she postulates are induced by disturbances in the functioning of the regulatory genes, but the causes of the failures are not specified.

where this limit is established. In particular, it cannot be excluded that the limited number of cell divisions is due to a decline in sensitivity to the growth factors, which, in turn, can be conditioned by the gradual accumulation of cholesterol in the plasma membrane, as occurs in the organism.)

Some examples are erroneously attributed to the category of programmed death (and aging), in which the presence of such a special goal is assumed. The Pacific salmon is one such example though it would be more correct to consider it an example characterizing the link between development (reproduction) and death, or an example of pleiotropism in the activity of the genes.

A relatively large group of aging theories is based on assessing the activity of the organism as a whole, i.e., on the so-called systems approach to the problem of aging. One of the branches of this approach in the modern epoch is cybernetics, the science of control and communication in different systems and, naturally, in living systems. In particular, it is worth noting here that concrete data on the neuro-endocrine system, viz., on the system of control in complex organisms, served frequently as the basis for more general conclusions in theoretical cybernetics, which later gained the features of an integral science that considered, first of all, the principles of control and interaction.

However, simple extrapolation from the general principles of cybernetics does not lead to elucidation of the mechanisms of aging. Cybernetics helps to understand how the system works, but without concrete data and concepts it cannot explain why the regulatory system ceases to accomplish its principal task during normal aging. The "systems theories" of aging, which are considered in gerontology, give no answer to this question either.

We have discussed briefly how the general concepts about the physical nature of the world varied the approaches to understanding the process of aging. Not everything gained earlier was rejected in the new spiral of accumulating knowledge. However, it would be wrong to assert, as do some researchers, that there exist at least 100 different theories of aging, or, to be more precise, 100 different concepts about this phenomenon. The majority of theories that can be found in the long historical list gradually lost their significance. Currently, there are essentially only a few principal approaches to the problem of aging that can be seriously considered, in particular, the probabilistic and deterministic approaches. But the very content of these general approaches has changed greatly in recent years.

Let's begin with the changes related to the class of probabilistic events that are associated with the accumulation of damage

in the cells and tissues of the organism with increasing age. These damaging agents are divided according to their origin into agents from the external environment and agents that originate owing to regular internal processes in the organism. In essence, only the accumulation of damage associated with external agents relates in the strict sense to probabilistic events. Examples of these effects are stress, various types of radiant energy (including ultra-violet radiation), chemicals (including carcinogens), etc.

Despite the considerable contribution of these factors to the general picture of aging, they are not the principal reason for aging. Without going into detail, it is easy to imagine the arguments that relate the external factors to the primary causes of aging.

Indeed, let's assume that the organism finds itself under ideal external conditions, which do not damage but actually protect it from unfavourable influences. Will no age disturbances in the activity of the organism occur in this ideal situation (e.g., the switching off of the reproductive function at a certain age)? Though an external factors can accelerate the approach of the climacteric, the absence of stress is unable to call it off. At the same time, the interest in the role of external factors that can undoubtedly influence the rate of aging is also

determined by the fact that the method of action of the external damaging agents closely coincides with the mechanism by which damage is inflicted by internal factors.

However, an important correction must be introduced here. The internal damaging events relate to probabilistic ones only to the extent that it is impossible to determine exactly "when and where" they will occur (e.g., in which cell or totality of cells, and exactly when). But the appearance of certain internal damaging events is a regular feature because it is inseparable from the properties of the "material" that "living matter" is made of and from the chemical (biochemical) processes occurring in the organism.

As far as the "properties of the material" are concerned, although there is continuous renewal in living systems and "atoms do not age", the already organized aggregates of atoms (i.e., molecules) can age on account of accumulated damage. An example of this kind is the joining together of large collagen molecules under the influence of by-products of metabolism, which, in particular, is one of the reasons for the formation of wrinkles.

Certainly, biochemical reactions have improved in the course of evolution, closely approaching "wasteless production", to use a modern industrial term, meaning the

maximal utilization of the by-products of metabolism. But for a number of reasons, which are impossible to discuss here in detail, biochemical processes cannot be totally perfect: beginning with a certain level of this perfect organization, a considerable increase in the number of genes would be required, whose function would be reduced to the elimination of associated reactions causing an unprofitable increase in the "energy cost" of maintaining the living system itself.

Therefore, alongside the creation of the necessary protective mechanisms during evolution, the principle of pleiotropic activity of the genes was "chosen". According to this principle, the genes and reactions (processes) controlled by them that provided advantages during the period of growth, development and reproduction of the organism, despite the emergence of undesirable, in particular, damaging, effects and consequences at a later age as a result of utilizing these processes, have been consolidated in the genetic code. But during this period the various types of damage did not tell on the indices of reproduction (and, therefore, were not eliminated by natural selection); they only induced a phenomenon that is now called "aging".

A vivid and significant example of this is provided by the analysis of phenomena associated with the evolutionary increase

in the capacity to utilize oxygen in energy processes. Let's consider this phenomenon in its most general form on the basis of the works of Academician N. M. Emanuel and such researchers as D. Harman and R. Cutler.

Life originated in an oxygen-free environment and the appearance of free oxygen was conditioned by vital activity itself. When the concentration of oxygen in the atmosphere reached 1%, which according to certain calculations occurred about 1.3 billion years ago, for the organisms that had "learned" to use oxygen in energy reactions found themselves in a toxic environment. But many living organisms managed to survive in an oxygen-containing atmosphere because they had already acquired protective mechanisms that counteracted adverse reactions arising during the utilization of oxygen, viz., free radical reactions.*

* Free radicals are atoms or molecules that have an unpaired electron. The unpaired electron makes them extremely reactive. Many mechanisms can cause the appearance of free radicals in cells, but more often and more intensively they make their appearance as unstable intermediate products of normal metabolism, e.g., in oxidation reactions, in reactions associated with the formation of ATP (adenosine triphosphate), which plays the role of a link between processes supplying energy and processes utilizing it. Free radicals often cause peroxidation of unsaturated fatty acids found in the structure of the cell membranes. This leads

The formation of free radicals in the organism during the pre-oxygen era was mainly due to the energy of the Sun, and the organisms that had more effective antioxidant mechanisms survived in the evolutionary process. These mechanisms were used for protection against free radicals that formed in reactions with oxygen. A series of antioxidant systems emerged in the course of evolution. Currently, about 20 systems and substances are known to possess antioxidant activity, among which a most essential role is played by a specific enzyme, superoxide dismutase. (This enzyme effects the regrouping of two molecules of superoxide with the formation of molecular oxygen and hydrogen peroxide, the latter is transformed into a molecule of water by means of the catalase enzyme.)

Damaging side effects of any biochemical processes are, according to the terminology

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to a disturbance in the cell's function, in particular, to injury to lysosomal membranes (containing the "splitting enzymes") and mitochondrial membranes (where the oxidation of energy substrates occurs). The accumulation of old-age pigment, lipofuscin, is also associated with the peroxidation of lipids and other compounds. Most importantly, the free radicals can interact with DNA and proteins, which can induce mutations and other damages to the genome, e.g., depression of "blocked" genes (see Chapter 10), or a disturbance in cell differentiation (its dedifferentiation), which is characteristic of aging.

used by R. Cutler, a source of the metabolic type of aging, and he designated the counteracting protective mechanisms as antiaging mechanisms. (Apparently, to popularize this phenomenon, V. V. Frolkis called it "vitauct", from "vita", meaning life, and "auctum", meaning increase. In: *The Biology of Aging*, Nauka, Leningrad, 1982, p. 6.) According to Cutler, the maximal lifespan for any species depends on the degree of effectiveness of the antiaging processes, given that all other conditions are equal. Some interesting data on the activity of superoxide dismutase in the tissues of 12 primates indicate that the longer the maximal lifespan in the species, the greater the activity of the enzyme. In other words, the more efficient the protection against adverse reactions that emerge during the utilization of oxygen, the later the age-related changes that cause death occur. Antiaging mechanisms determine the species lifespan, given that all other conditions are equal.

Attention should be given in this respect to one very important circumstance. The term the "species lifespan" generally means the average length of life characteristic of each species as is recorded in the genes. However, it was found that the maximal lifespan characteristic of representatives of a given species is correlated with the rate of death of the animals in the natural habitat when external factors are the cause

of death. This type of correlation has been studied most thoroughly for birds. The conclusion is drawn that the internal mechanisms that determine the death of the organism, e.g., the process of metabolic aging and antiaging, evolve to the degree that is determined by the real lifespan in natural conditions. From this point of view it now seems appropriate to replace the term the "species lifespan" by the term the "maximal lifespan".

As stated above, no protective system can ensure absolute protection. It is for this reason that with an increase in chronological aging there is an increase in the quantity and pronouncement of damages, among which damage to the genetic apparatus, first and foremost, DNA, has great significance. Though this phenomenon lies at the basis of mutations, which is a necessary condition for evolutionary variability, it should be restricted as much as possible in the case of the sex cells as well as the somatic ones, because the accumulation of mutations in both the former and latter can lead to death of the cells and to changes in their vital activity, e.g., due to the development of auto-immune lesions (Chapter 9). Accordingly, to remedy defects in genes, there are systems for repairing DNA, which in the given context can be considered to be antiaging systems.

As it has been noted by the American

radiologists R. Hart and R. Setlow there is actually a tenfold difference in the rate of repairing DNA between short-lived and long-lived species. Recently, a more than twofold difference has been found between two close species of rodents with different maximal lifespans.

Thus, alongside the metabolic process of aging, there exists and functions a process (and mechanisms) of antiaging. One could say that the organism "contains within itself" both processes.

The concept of "antiaging" is very important from one more point of view. As we already know, the diverse symptoms of aging represent a psychological obstacle in seeking its key mechanisms. But if the various symptoms of aging, e.g., joining of collagen molecules and damage to DNA (that can secondarily induce most diverse changes), depend on the effective functioning of only two elements of the metabolic antiaging mechanism (extinction of free radicals and repair of DNA), then there are grounds to study the aging mechanisms not through the secondary (external) symptoms of aging, but by more general and, correspondingly, more fundamental processes. As a result, the search for the causes of aging narrows.

But the metabolic causes of aging are not restricted to metabolic phenomena. Another category of phenomena relates to

the development of the individual organism, i.e., to ontogenesis.

Proceeding from purely speculative and generalized concepts, it seems natural to consider aging as the continuation of development, i.e., as one of the stages of ontogenesis. But, despite the obviousness of this approach, it is highly vulnerable to criticism, because it follows that aging (as a part of ontogenesis) is just as programmed as the development of the organism. Meanwhile, if the pressure of natural selection is taken into consideration, there are no grounds to agree with the existence of an aging program (see Introduction). Therefore, the idea of combining the early (useful) and the late (damaging) effects in the activity of the genes—the idea of pleiotropy, multiplicity, the activity of one and the same genes—was applied to elucidate not only metabolic aging, as was discussed above, but also aging associated with the mechanism of development.

The main observations that are commonly presented to illustrate the latter mechanism relate to data indicating that restriction of the caloric value of the diet causes delayed sexual maturation (i.e., delayed development of the organism), which, in turn, is combined with retarded aging and, correspondingly, increased maximal lifespan. Such experiments, however, are also vulnerable to criticism because restriction

of the caloric value of the diet renders a favourable effect if it commences after the end of the development phase (after the first year of life in experiments on mice). In addition, when strictly considering the phenomena, it seems impossible to discriminate the influence of reducing the caloric value of the diet on aging via metabolic mechanisms (see above). But data comparing different species also indicate that the shorter the period of development and sexual maturation in a species, the shorter the maximal lifespan, and vice versa. Thus, in particular, the longest period of sexual maturation and the maximal lifespan among all mammals is observed in humans.

Hence, though the connection between the rate of development and rate of aging is still unclear (see below), two basic mechanisms of aging are currently outlined: the first is the metabolic mechanism, and the second is associated with the developmental mechanism of the organism.* In other words, according to Cutler, aging is

* We stress once again the advantage of this approach, which makes it possible to consider the following phenomena as not individual or separate (and correspondingly, theories of aging): the joining together of protein macromolecules or DNA; somatic mutations, in particular, in the cells of the immune system; the catastrophe of error accumulation in protein (enzyme) synthesis; the death of cells as a result of damage; free radical reactions, or DNA depuration, etc.

a by-product of metabolism, development, and differentiation in the organism. Cutler introduces an additional component into this system, viz., antiaging processes. But the "aging-antiaging" process is not limited to only these components. One more component is added to this scheme on the basis of the following considerations.

The indices of metabolism, aging, and functions significantly coincide in all the mammals, including humans. They are still more uniform in higher monkeys. For example, 99% of the proteins in the human and the chimpanzee are identical. At the same time, the maximal lifespan of the chimpanzee is two times less than that of the human. Both the secondary symptoms of aging as well as the primary mechanisms of this phenomenon associated with metabolism and development coincide in higher organisms. Comparing these data, Cutler comes to the conclusion that there is a fourth component in the general system of aging, viz., a component of "longevity". His arguments, founded on numerous data, including archaeological data, are based on examples relating to the evolution of the animal world, especially, primates, and most importantly, humans.

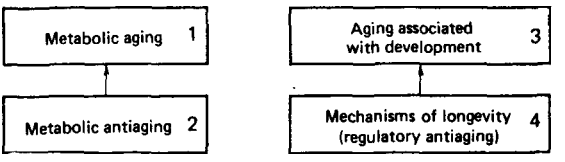
A gradual increase in the maximal lifespan is observed during evolution, which is traced over a period of 60 million years of evolution of primates. The rate of change

in this index is very high in the ancestors of modern humans over a stretch of about 1.5 million years, and exceptionally high (an increase of 14 years over a period of 100 000 years) about 100 000 years ago. Then the process of prolonging the maximal lifespan stops entirely. Calculations demonstrate that the number of useful (adaptive) mutations during 100 000 years of rapid increase in this index could range from about 160 to 250 (a human has about 40 000 genes). If this small percent of mutations causes such a great increase in the lifespan, then it is quite natural to conclude that these mutations occurred in the system of regulatory genes. In other words, the effectiveness and rate of the processes changed, but not their structure owing to the addition of new properties.

What the processes actually consisted of remains unclear though some external indications of these changes have been determined. First of all, within a series of related species of organisms, in particular, the primates, the greater the size of the body and the brain (and both these factors exert an effect independently of one another) the greater is the maximal lifespan. The latter made it possible to establish a simple mathematical dependence between the stated parameters; a close correspondence is observed between the data predicted by the formula and the observed maximal lifespan.

Already in 1965, G. Sacher assumed that the dependence of the index of longevity on the mass of the brain could be understood as an indication of some systems effect, apparently, as an indication of improvement in the homeostasis. This assumption commonly meets with objections because there is no evidence of less effective homeostatic regulation in, for example, a rat as compared to a monkey or a human. (This objection requires a broader assessment. For example, though it is known that rats, as a species, are distinguished by high adaptivity, which supposedly ensures their survival in the most difficult conditions, severe disturbances originate in these animals in experiments where they are subjected to such stresses as a shrill sound or a "stationary pose".)

Hence, four components, forming two blocks, *A* and *B*, can be pointed out in Cutler's theory of aging, which has been most profoundly elaborated in regard to mammals:



It's obvious that component *B*-3 corresponds in name to the ontogenetic model of

aging that the author of this book has been elaborating for a long time.* At the same time, the coincidence is only seeming in many aspects.

First of all, the ontogenetic model considers the mechanism per se that determines the transformation of the developmental program into the aging mechanism (see Chapters 4-6), while in modern gerontological conceptions (not to mention still older views) concrete mechanisms escape consideration. Second, regularities follow directly from the ontogenetic model of aging. They determine the onset of certain diseases, which form the group of major (noninfectious) human diseases due to their association with the mechanism of development and aging. At the same time, the mechanisms

* This author believes that any suspicions of borrowing must be dispelled. Though the term "ontogenetic model" of aging and of the associated diseases appeared in print for the first time only in 1983 owing to the suggestion of the editor of the author's book *The Law of Deviation of Homeostasis and Diseases of Aging* (Boston, 1981), in which a new model in medicine was discussed (naturally making it necessary to give a name to this model, see Chapter 12), the regulatory principle itself of the transformation of the organism's developmental program into an aging mechanism was described by the author in 1971 (*Lancet*, 1971, 1, pp. 1211-1219), and in a Soviet publication for the first time in 1958. Cutler first mentioned these ideas in 1972, and only from 1976 to 1978 did he use terminology pointing to the association of aging with development.

considered in modern gerontological theories do not directly demonstrate this association for many diseases of this group, e.g., age-related mental depression, or the climacteric. Finally, the ontogenetic model makes it possible to combine both components in block *B* into one, forming a single mechanism of regulatory aging and anti-aging. Let's first consider this problem as applied to the formed type, i.e., to the mechanism of ontogenesis, and then to phylogenesis.

The lifespan of different individuals varies considerably and, at the same time, there is a regular logarithmic increase in the mortality index with age (see Fig. 6). In light of the ontogenetic model, these variations are conditioned by different rates of development, aging, and appearance of age-related diseases, and, in turn, all these phenomena depend greatly on the rate of regulatory—mainly hypothalamic—changes. To illustrate this, let's analyze several examples (Table 5).

Let's imagine the case where from early childhood on a person receives a surplus amount of calories in the diet, which results in obesity (Table 5, item 3). As is known, accelerated development may occur as a consequence of this (Chapter 14). Early switching-on of the reproductive function is an indication of acceleration (similarly, excessive feeding of animals accelerates

Table 5. Mechanisms of Natural Selection, Rate of Ontogenesis, Age-Related Diseases, Species Lifespan

Factor	Type of change	Mortality	Hypothalamic threshold	Duration of maturation	Development rate of age-related diseases	Species lifespan
External causes of death ↑*	Phylogenesis	↑***	↑	↓	↑	↓
External causes of death ↓**	Phylogenesis	↓***	↓	↑	↓	↑
Diet ↑	Ontogenesis	↑	↑	↓	↑	—
Diet ↓	Ontogenesis	↓	↓	↑	↓	—
Illumination ↑	Ontogenesis	?	↑	↓	↑	—
Estrogenic signal ↑	Ontogenesis	?	↑	↓	↑	—

Note: ↑* — increase; ** — decrease; *** — from external factors.

their sexual maturation). Owing to the fact that the mechanism of sexual maturation is linked with an elevation in the hypothalamic threshold (Chapter 5), the conclusion can be drawn that an increase in the rate of hypothalamic shifts is observed in this situation,

At the same time, it follows from the ontogenetic concept that certain phenomena of aging (and age-related diseases) represent a direct continuation of the developmental mechanism. From this point of view it is possible to explain why accelerated age-related pathology and, consequently, a shorter lifespan are observed when there is a higher rate of hypothalamic changes in early ontogenesis, i.e., during accelerated sexual maturation. Thus, the indication of longevity of an individual organism depends on the state of the regulatory systems. It follows also from Table 5 (item 4) that opposite changes occur during restriction of the caloric value of the diet in the pre-reproductive period.

Let's consider one more case (Table 5, item 5). As is known from experiments on rodents, excessive illumination in the pre-reproductive period accelerates sexual maturation, and it has been shown experimentally that there really is an elevation in the hypothalamic threshold under these conditions, i.e., an increase in the rate of hypothalamic changes. Correspondingly, the incidence of age-related diseases, in particular, cancer, also increases at an earlier age. At the same time, excessive illumination during the period of sexual maturity accelerates the age-related switching-off of the reproductive function (it also accelerates hypothalamic changes and elevates the

hypothalamic sensitivity threshold to the sex hormones). Hence, one and the same effect (excessive light) may cause the early switching-on and the early switching-off of the reproductive function because the rate of realizing one and the same hypothalamic process increases in both cases.

It follows from these examples that the relationship between the duration of the prereproductive period to the total lifespan is determined in the ontogenesis of each individual by the same regulatory process, and the rate of realizing hypothalamic shifts (rate of realizing the law of deviation from homeostasis, Chapter 3) is the main element in this process.

Let's now attempt to estimate whether this criterion can be applied to explain the constancy of the ratio between the duration of the prereproductive period (PP) (or duration of growth period) to the maximal lifespan (ML) in various species, i.e., in phylogenesis.* The ML:PP ratio for humans is about 5:1, i.e., 100 and 20 years, respectively. Though the index is not necessarily 5 in other species, it characterizes a regular correlation between the duration of these two periods of ontogenesis, which demands assessment of the given phenomenon in light of the requirements of natural

* Phylogenesis—evolutionary history (dependence) of the development of a species.

selection. This assessment is very important because it makes it possible to discriminate between the influence of metabolic and regulatory aging.

When solving this problem, let's consider also the difference in the rate of hypothalamic changes in the ontogenetic and phylogenetic aspects. To reveal the role of this criterion in the ontogenetic aspect, it is sufficient to observe the changes during the lifespan of one individual, e.g., to determine the association between the rates of development and aging in experiments on rodents with a restricted diet. Conversely, it is possible to reveal the role of this criterion in the phylogenetic aspect only when assessing it over the course of generations, which requires the application of natural selection criteria. Let's now analyze two cases, applying to each one the concepts of metabolic and ontogenetic mechanisms of aging.

In the first case there is an increase in the death rate of the animals owing to external causes and, consequently, a decrease in the actual lifespan of the specimens as a whole population (Table 5, item 1). Since natural selection is always directed toward survival of the species, specimens with a decreased prereproductive period, i.e., with a higher rate of sexual maturation, have an advantage because they have an increased probability of leav-

ing a greater number of offspring despite a decrease in the actual lifespan. At the same time, a decrease in the maximal lifespan is observed if the duration of the lifespan is conditioned by metabolic aging, because metabolic antiaging stops being a selective factor (a factor by which selection occurs), since it presents no advantages, given a decrease in the actual lifespan due to external causes. In the final end, the value of the ML:PP ratio is preserved. Hence, in the given case, the idea of metabolic aging corresponds to the real state of affairs in phylogenesis.

The ontogenetic mechanism of aging corresponds to this criterion. As shown here, natural selection acts in the direction of "picking out" specimens with a higher rate of increase in the threshold (because early switching-on of the reproductive function increases the probability of leaving progeny when the lifespan is shortened), and given a higher rate of increase in the threshold, a decrease in the value of the maximal lifespan (due to the more rapid development of "normal diseases") occurs, and as a result the value of the ML:PP ratio is preserved.

However, analysis of the second case (when the conditions favour the life of the species, and as a result, the actual lifespan increases) on the basis of the ontogenetic model reveals preservation of the value of the ML:PP ratio, while the principles on

which metabolic aging is based do not correspond to the given requirement (Table 5, item 2). Indeed, given favourable living conditions, which ensure a later occurrence of death from external causes (i.e., in situations with an increase in the actual lifespan), metabolic antiaging turns into a selective criterion: the later aging occurs, the greater the potential of leaving numerous offspring. But in this case the mechanism affecting metabolic processes should not lead to prolonging the duration of the prereproductive period, because under more favourable living conditions, earlier sexual maturation is more advantageous because it ensures additional potential to increase the number of offspring.* As a result, the ML:PP ratio should be shifted in the direction of its increase. But, the fact that this ratio is stable for each species indicates that in the second situation it is impossible to base the origin of this stability on the phenomenon of metabolic aging and antiaging.

On the other hand, the mechanisms of ontogenetic aging correspond to the latter criterion as explained by the following. Specimens with a slower rate of increase

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* More complex mechanisms, assuming that metabolic aging (and, correspondingly, antiaging) influences the rate of realizing regulatory (ontogenetic) aging, are not considered here (see below).

in the hypothalamic threshold, which ensures a longer lifespan and the potential of leaving more offspring, gain advantage under favourable conditions, i.e., in case of a longer actual lifespan. Consequently, this criterion becomes a selective one. But it is automatically combined with a decrease in the rate of increase in the hypothalamic threshold of the prereproductive period because both of the latter parameters represent, on the whole, one and the same phenomenon. Therefore, though retarded sexual maturation is a negative indication, if it reduces the reproductive potential (nonselective potential), it inevitably follows from the considered regulatory mechanism of aging. As a result, the value of the ML:PP ratio remains the same, or is reduced. At the same time, in this situation an increase in the actual lifespan ensures an increase in the number of offspring despite retarded sexual maturation.

Data point out that a prolongation of ML has been observed in the evolution of primates for at least the last 60 million years. As stated above, this index in humans increased most substantially over the last 100 000 years (R. Cutler, 1980). In light of this the following conclusion seems very interesting: a value of 5 for the ML:PP ratio is minimal for mammalian species. These data demonstrate that the increase in ML combines with a decrease in the rate

of development.* This phenomenon, called "neoteny", which means prolonged childhood, corresponds to selection by the regulatory (ontogenetic), but not the metabolic, type of aging when it combines with an increase in ML.

Now, let us attempt to assess the theories of aging on the basis of what has been stated above. If we refer again to the graphical representation of the most modern gerontological theory (or, at least, to the latest one, which considers the previous experience of other theories), it is possible to draw the following conclusions.

First of all, when comparing the significance of block *A* (metabolic aging) and block *B* (regulatory aging), it follows that, despite the existence of both types of processes, regulatory aging is controlled by natural selection in a greater number of situations, and, correspondingly is of greater evolutionary significance (because the evolution of primates followed the direction leading to an increase in the maximal lifespan). Hence, block *B* is of key significance in this diagram.

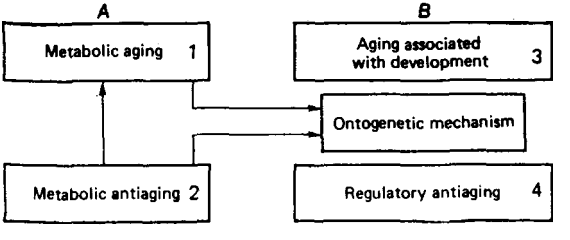
Secondly, when putting together block *B*, a separate subsystem—*B*-4, i.e., mechanisms of longevity (or regulatory antiaging),

* For example, it is noted that the human has more features of "childishness" at all stages of development than the chimpanzee, a related species, whose ML is one-half of that of the human.

must be introduced. According to the ontogenetic model, the regulatory mechanisms of aging and antiaging are realized in the same way in ontogenesis and phylogenesis, viz., on account of the deceleration or acceleration of one and the same process (common for the periods of development and aging), by means of which the law of deviation of homeostasis is realized. The main element in this process is the change in the hypothalamic sensitivity to the regulating homeostatic signals in the systems of the reproductive, energy, and adaptational homeostats.

In the epigraph to his work of 1976, where he presents his generalized theory for the first time in detail, Cutler quotes the following statement made by Albert Einstein, "A theory is the more impressive, the more simple its premises, the more different the type of objects it is related to, and the wider the range of its application".

If the criterion of maximal generality with maximal simplicity is observed, then, considering the ontogenetic mechanism, the diagram of the aging theory should be as follows:



Third, it can be noted that there is a relationship between blocks *A* and *B* in the ontogenetic mechanism, unlike the four-component diagram wherein the metabolic and regulatory blocks co-exist independently. Let's refer once more to Table 5, (item 6) to consider the principle of this relationship.

It is known that a single injection of estrogens (female sex hormones) accelerates the sexual maturation of a sexually immature animal during a certain period of its life. Among many variants, the following interpretation on the origin of the effect is quite acceptable. Estrogens intensify the synthesis of neuromediators, primarily, dopamine, in the hypothalamus. It is now known that free radical reactions commence in the process of dopamine synthesis and turnover (i.e., in the metabolic turnover of catecholamines). It has been suggested that in this case the cells of the hypothalamic sex centre are damaged (or activated) and this is manifested by an elevation in the sensitivity threshold of the centre and accelerated sexual maturation.*

* Evidence of the reality of this phenomenon, when realization of the function induces deviation of homeostasis, is provided by data demonstrating that the application of estrogens to girls with an inborn lack of ovaries induces an elevation in the hypothalamic sensitivity threshold to estrogens. This phenomenon also fits the "cascade mechanism of aging" suggested by C. Finch (1976), an Ameri-

When sexual maturation accelerates under the influence of surplus nutrition, a similar mechanism can participate in this complex effect, since the greater the generation of energy and the more intense the functioning of the metabolism, the greater the "output" of free radicals. M. Rubner's constant (see above) can be interpreted from this point of view, viz., the caloric consumption is associated with the lifespan because the energy processes influence the metabolic and the regulatory components of aging.

Thus, it is possible to outline the existence of an association between the probabilistic and deterministic mechanisms of development and, correspondingly, aging within the limits of the ontogenetic model. This is a necessary step forward on the path toward integration in biomedicine.

In addition, adaptation to external unfavourable factors, which influences the index of mortality in the population, is realized on account of changes in the hypothalamic sensitivity threshold to the regulating signals, which significantly determines the diverse vulnerability to stress and diseases in young and old animals. Let's examine a well-known case from the works of J. Christian (1976).

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can neurophysiologist. He and co-workers later pointed out (1983) that the removal of estrogens from experimental animals slowed down the development of age-related hypothalamic shifts.

When the density of a population reaches a certain value, e.g., due to increased birth-rate, the secretion of the main stress hormones, corticotropin and corticosterone, increases in the animals. On the one hand, these hormones reduce the immunity, thereby increasing mortality as a result of infections and parasitogenic diseases; on the other hand, the reproductive function is retarded by the effect of the adrenocorticotropic hormone (ACTH) on the hypothalamic sex centre. The degree and duration of the elevation in the level of the stress hormones as well as the degree of sensitivity of the sex centre to suppression are conditioned by the age of the animals subjected to population stress. The state of stress persists longer in old animals owing to resistance to suppression, which lies at the basis of hyperadaptosis (Chapter 4), while in young animals it is shorter owing to the greater sensitivity to suppression, although the capacity for reproduction is suppressed more significantly. As a result, more old animals die, while young ones reproduce less. The optimal size of the population is recovered, and the potential for reproduction is preserved in the young animals, given the emergence of favourable conditions. It is obvious that the metabolic processes of aging and antiaging do not provide such possibilities for adaptation.

Hence, proceeding from the concept of

the ontogenetic mechanism of development and aging, the following conclusion is quite natural. The single measure that can determine both the rate of regulatory aging of an individual and the differences in the maximal lifespan of individual species with similar physiological characteristics (e.g., in mammalian species) is the rate of realizing the law of deviation of homeostasis, or, which is almost the same, the rate of hypothalamic changes.

From this point of view, a decisive experiment can be suggested to assess the plausibility of the phylogenetic aspect of the ontogenetic model. If the model is correct, the experiment should demonstrate an inverse relationship between the maximal lifespan of the species and the rate of changes in the hypothalamic threshold. In other words, the greater this rate, the less is the maximal lifespan in a group of related species.

As far as applying the ontogenetic model to the problem of aging, there should be nothing unusual about this. Proceeding from general considerations, some scientists imagine aging as a part of ontogenesis, and the novelty of the ontogenetic model is stipulated in this relation by describing the hypothalamic mechanism of interdependence between development and aging. But the fact that the by-product of the developmental program is not only aging

but also certain diseases, viz., the major diseases of human beings (and of higher animals), is not perceived within the framework of traditional gerontology.

To understand the existence of such contrary opinions on the association between aging and a certain group of diseases, a more general question must be answered: what is the cause of diseases in general? This will be discussed in the next chapter.

Chapter 12

Four Models of Disease Development

> The following riddle must be solved: if all the known diseases are induced by casual circumstances that may or may not happen, why do strictly specific diseases develop in an individual in the course of aging, i.e., why is it that alongside the casual there are also regular causes of some normal diseases? We can't prevent the approaching crisis in modern medicine without the answer to this question.

The establishment of groups and classifications is an eternal striving for any science, and medicine is not an exception. Various principles of classifying diseases have been applied at different stages of development of medicine: 1) by its location; 2) by the manifestation of a pathologic process; 3) by a causative factor; and 4) by the mechanism of development. Examples relating to the first principle include atherosclerosis (disease of the arteries), diabetes mellitus (disease of the pancreas), pneumonia (disease of the lungs), etc. The "local" principle of classification does little to elucidate the essence of diseases but it has contributed to the development of modern specializations in medicine with its positive and negative features. Thus, specialists appeared gradually, viz., cardiologists (heart and vessels), pulmonologists (lungs), gastro-

enterologists (digestive tract), hepatologists (liver), nephrologists (kidneys), urologists, endocrinologists (glands of internal secretion), etc.

Classification according to the manifestations of the disease led to the differentiation of three major types of diseases, viz., inflammatory, degenerative, and tumorous. For example, for the liver, the following diseases correspond to this classification: hepatitis, cirrhosis, and cancer. There is a certain logic in this division, especially if it was possible to consider the mechanism of development of the disease, i.e., pathogenesis. For example, in various inflammatory processes, e.g., hepatitis, rheumatic carditis, and iridocyclitis (inflammation involving the iris and the ciliary body), are often treated with the same medical means—anti-inflammatory hormones.

But the first as well as the second principles of classification did not reveal the *causative factor* of the diseases, which seriously limited the elaboration of medical and especially preventive measures.

Therefore, the third approach to the classification of diseases, viz., the one based on causation, is of independent significance and a necessary supplement to the other two approaches. If the other approaches answer the question of "where" and "how" a disease manifests itself and emerges, this approach attempts to find out "why" it emerges and,

consequently, how the development of the process can be prevented. It corresponds to the etiological approach (*etio* meaning cause) in the classification of diseases.

As stated in the Introduction, over the course of development of the natural sciences and, correspondingly, the biomedical sciences, ever new causes of diseases have been revealed. But though at first sight this may seem to be a strange result of long and profound efforts, the data currently available can be combined into only two subgroups of phenomena, viz., external, i.e., ecological causes of diseases* and internal (genetic) causes of diseases.

Indeed, all the diseases known to medicine can arise due to the influence of factors that are external to the organism, viz., physical trauma, bacteria, viruses, protozoa, fungi, ionizing radiation, toxic substances of biological or artificial origin, mental and physical overstrain caused by stress, malnutrition, overeating, or incorrect nutrition, etc. There is nothing superficial or unusual in this classification because a living organism does not exist by itself but in interrelationship with the environment to which all the other living creatures and the entire "physical" world as a whole

* Ecology is the science concerned with the interrelationship between organism and the environment.

relate. Thus, in modern medicine the main model for the development of diseases is the *ecological* model*.

But beyond all question there is a second model for the emergence of diseases, viz., a model in which various inborn (genetic) defects are the cause.

The common character of the genetic code convincingly illustrates that the living world is truly a single entity and that, correspondingly, there is an interaction between its components. In the chain of this interaction, natural selection and diseases (as one of the tools of natural selection) characterize in concrete form the influence of the external environment on the development of living organisms (see Chapter 11).

The human is considered to have from 40 000 to 80 000 structural genes. Damage inflicted on the structure of the sex cell genes causes disturbances in the activity of the organism if these disturbances are compatible with the preservation of life. More than 2600 genetic diseases are known to be associated with damage to the genetic structure, and about 80 diseases are condi-

* The American pathologist F. Ludwig (1980) considers that the ecological model is not the main model but the only model of modern medicine, which gives the following answer to the question, Why do diseases spring up?: because organisms are damaged by external factors.

tioned by disturbances in the chromosomes.

For example, there are genetic defects in the complex mechanism of synthesis, transport, and utilization of lipoproteins, which are the carriers of triglycerides and cholesterol that cause premature development of atherosclerosis (see Chapter 9). In particular, so-called familial hypercholesterolemia is one such case in which the genetic defect is associated with the absence (or decrease in the number) of receptors of low-density lipoproteins on the cell membrane. Atherosclerosis and other diseases can also emerge prematurely when there are genetic defects in the structure of the carrier-proteins of cholesterol and triglycerides (apoproteins) or when genetic disturbances cause a deficiency in lipoprotein lipase, an enzyme responsible for the catalysis of lipoproteins and removal of fatty complexes from the blood. In other words, inborn defects are possible in any physiological system and may cause the emergence of diseases in the absence of unfavourable ecological influences and long before the age at which diseases with similar symptoms are found in people not suffering from the corresponding genetic defects.

Thus, a *genetic* model of disease development exists alongside the ecological model. Certainly, each individual genetic breakdown occurs quite rarely, but the sum total of all such defects is a significant number,

For example, approximately 10% of premature atherosclerosis in any large group of people is conditioned by various types of inborn disturbances in metabolism. Therefore, if the models of disease development are not differentiated, confusion is inevitable when assessing the role of age in the development of atherosclerosis. And conversely, the idea of ecological and genetic models assists in seeking the concrete cause in each case of premature development of the disease.

Table 6 shows that for all the major (noninfectious) human diseases there are diseases related to them by their clinical symptoms, and the ecological and genetic factors are of key significance in their development. But the specific feature of all the major diseases, or, to be more precise, the feature responsible for their being dominant is the fact that it is not accidental but obligatory processes that form the major diseases irrespective of the genetic and ecological influences.

Concrete data on the regulatory shifts that cause the development of the major human diseases have been given in the respective chapters. In general, it is possible to state that the major diseases in this system of views are a by-product of the mechanism of development of the organism (ontogenesis). In compliance with the latter, it is necessary to distinguish

Table 6. Models of Medicine (Some Examples of the Development of the Main Diseases)

Ecological	Genetic	Ontogenetic	Involutional (accumulational)
Causes: damaging factors of external environment. Prophylaxis: elimination of external damaging factors.	Causes: genetic defects. Prophylaxis: elimination or compensation of defect.	Cause: mechanism of organism's development. Prophylaxis: deceleration of development and aging.	Cause: accumulation of defects and damages. Prophylaxis: intensification of activity of DNA repair systems, antioxidation systems; deceleration of metabolism, etc.
Atherosclerosis caused by overeating.	Atherosclerosis caused by familial disturbances in the turnover and transport of lipoproteins in the cell.	Age-related changes in metabolism conditioning development of atherosclerosis.	Atherosclerosis conditioned by damage to vascular walls by by-products of metabolism.

Table 6 (concluded)

Ecological	Genetic	Ontogenetic	Involutional (accumulational)
Cancer caused by carcinogenic chemicals, viruses, ionizing radiation.	Familial polyposis, Blum's syndrome, xeroderma pigmentosum, etc., increasing probability of cancer.	Age-related cancrophilia.	Mutation and damage to chromosomes conditioned by by-products of metabolism.
Accelerated aging caused by carcinogens, stress, irradiation, and overeating.	Progeria, Werner's syndrome.	Normal aging.	Accumulation of cell damages, cholesterol, lipofuscin, etc.

the third model of development of diseases, the *ontogenetic* model (Table 6).

Of course, some of the major diseases, e.g., atherosclerosis, develop very slowly under favourable ecological factors. Conversely, the rate of emergence and the pronouncement of atherosclerosis (and other similar diseases) increase so greatly under unfavourable environmental conditions that many major diseases are today considered to be the diseases of civilization. But though this notion is widespread, it is incorrect because it restricts the mechanisms of disease development to only external factors, which, in reality, just accelerate or decelerate the emergence of the major diseases by influencing the physiological basis of the disease. In addition, the classification of major diseases based only on the ecological principle does not cover such states as the climacteric and aging, while the major diseases are characterized most of all by the fact that they represent a group of interrelated diseases. The latter property is most important for understanding the origin of the major diseases as a whole and for distinguishing them as a separate category of the ontogenetic model of their formation.

Actually, there is an individual cause for each disease in the ecological and genetic models, e.g., for atherosclerosis it is overeating and a disturbance in the production

of lipoproteins in the liver. Correspondingly, different measures for the prevention and, frequently, the treatment of diseases are necessary in accordance with the various causes of their origin.

Conversely, in the ontogenetic model, all the diseases are interrelated. For example, there is profound "intertwining" in the mechanisms of the climacteric, hyperadaptosis, and mental depression, which is conditioned by the role of the decreasing concentration in hypothalamic neuromediators in the development of these diseases. Likewise, the role of surplus insulin is retraced in the mechanisms of age-related obesity, prediabetes and type II diabetes mellitus, metabolic immunodepression, atherosclerosis, and even cancrophilia. This mutual interpenetration of the major diseases significantly erases the boundaries between them, while all the earlier classifications of diseases are based on an opposite principle, viz., delimitation of each disease from all the others.*

And what is more, it has been necessary to isolate three new diseases (i.e., earlier unnoticed ones), viz., hyperadaptosis, metabolic immunodepression, and cancrophi-

* The concept of the "intertwining" of many diseases with one another and, as a result, the errors in modern classifications of a series of chronic diseases is developed by L. Stoddard (1980) based on other considerations.

lia, in the process of establishing links between the major diseases of humans in conformity with their ontogenetic model of origin, while the climacteric and aging were ascribed to the category of "normal diseases". (Arguments and data concerning all that stated above are given in the respective chapters of this book.) Without new diseases it would be impossible to retrace the relations between the major diseases with the completeness ensured by the ontogenetic model. Apropos, the diverse pathogenic role of overeating (or obesity) is just the consequence of the real relationships between the major diseases that are revealed in the ontogenetic model of their development.

The ontogenetic model establishes connections not only between the major diseases but also between the latter and certain mechanisms of aging. Within these mechanisms, one and the same elements are revealed that lie at the base of each of the ten major diseases. This indicates the absence of definite boundaries between aging and the major diseases, or, speaking in a more general form, between what is normal and what is pathologic. Therefore, aging is not simply a factor contributing to the development of certain diseases, e.g., the development of atherosclerosis, as is explained in traditional gerontology (see Chapter 11); rather, it bears elements that

are necessary for the development of atherosclerosis. A similar conclusion can also be drawn in regard to the other major diseases.

Thus, in summary, it is possible to say that the major diseases exist because their presence is determined by the mechanisms of development of the organism, and is, in essence, a by-product of the activity of this mechanism. Let's stress once more that it is not the disturbance of the law of constancy of the internal environment of the organism but precise realization of the law of deviation of homeostasis that determines the appearance of age-related diseases. If the diseases do not emerge at a certain period of life, this points to a deviation from the norm. In this sense, all the major diseases are "normal diseases".

In many aspects natural death is regulatory death: in many, but not all aspects. At the same time, there are factors that induce various types of damage to the cells, tissues, and regulatory systems themselves. The role of these factors in the development of diseases has been previously discussed (Chapter 11) in the examples relating cancrophilia and cancer, and the mechanism of aging. Certainly, the effects of the external and internal impairing factors partially coincide, owing to which, it would seem, there is no need to distinguish them in different models of disease development. Thus, for example, a carcinogenic

chemical that penetrates the organism from the outside and free radicals that originate as a result of normal metabolism may cause, in principle, impairment of the genetic apparatus of the cell with similar consequences that lead to the development of a malignant tumour. But the notion of a model of disease development includes not only a classification of the causes, but also a classification of the measures of prevention, which in these cases are principally different.

According to the ecological model, the external damaging factors must be eliminated. This method of prophylaxis is, however, of limited significance in decreasing the influence of the internal impairing agents. It is possible to strive for a rational diet, to eliminate its excesses (this reduces the rate of metabolic formation of internal damaging factors), yet a certain level of accompanying side reactions is inevitable. Other sources of internal damage are also inevitable. For example, impairment of the internal layer of the blood vessels (endothelium) is periodically caused by vortices in the bloodstream, which contributes to the development of atherosclerosis.

Naturally, the amount of damage due to internal factors increases, and unfavourable consequences accumulate in the course of time, i.e., in the process of aging. Therefore, even if one were to imagine an unrealistic

situation in which all the unfavourable external factors are eliminated, defects would continue to accumulate in the organism in various tissue, cellular, and subcellular systems, and consequently diseases would develop. It is now believed without a doubt that the internal damaging factors can and do play an independent role as causative agents in the mechanism of development of cancer, atherosclerosis, and aging itself.*

Let's assume that we have learned to eliminate these diseases and their consequences but are unable to completely eliminate the accumulation of damage in each structure of the cell and in each cell. This damage and its consequences then inevitably accumulate during aging. One of them, viz., the accumulation of age-related pigment, lipofuscin, has been mentioned in the chapter on the mechanisms of aging. Theoretically, the accumulating lipofuscin should have a most deleterious effect in nondividing cells, e.g., muscle and nerve cells. The functioning of these cells should worsen with the accumulation of lipofuscin.

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* And what is more, the damaging effect can proceed from the physiological (biochemical) processes per se (Chapter 11). Thus, for example, female sex hormones (estrogens) can damage the cells of some hypothalamic nuclei, which, in turn, can induce a certain type of benign tumour of the pituitary gland with age.

For example, it has been found that up to 50% of the cell volume in old drosophilas may be occupied by lipofuscin, and it is possible to imagine the situation that arises when a cell simply stops functioning and existing owing to the ballast contained inside.

Certainly there are other variants of accumulating damaging effects or substances, e.g., an accumulation of cholesterol in cell membranes (Chapter 9) and, correspondingly, new symptoms of pathologic processes, i.e., the emergence of new diseases. The features of such "future diseases" can be partially foretold, but they can hardly be accurately described because the character of their manifestation will preserve the probabilistic principle of accumulating damage.

But, in essence, the mechanisms of the fourth—*involutional*—model of development of diseases are just as real as the existence of organisms with their metabolic and other physiological processes that gradually create an accumulation of damage in the organism. Therefore, involutional pathologic factors function alongside the pathogenic factors described in other models of development of diseases. The following example is quite illustrative in this respect. Atherosclerosis usually originates in young people against the background of a high level of cholesterol in the blood, which is conditioned either by genetic defects, or an irregular way of

life. Here we are dealing with the genetic or ecological models of development of atherosclerosis.

The case is different however, when the clinical symptoms of atherosclerosis, e.g., myocardial infarction, appear between the ages of 60 and 65 or later. There may be no difference between the cholesterol content in the blood of the patient and in a healthy man of the same age. Sufficiently pronounced changes have already accumulated in the vascular wall, which contribute to the development of atherosclerosis irrespective of the cholesterol content in the blood. Therefore, the existence of the fourth accumulational, or involutional, model of disease development can be substantiated today though medicine is yet unable to assess in each concrete case the relative contribution of the mechanisms of this model in the development of diseases. But later, with increasing liberation from the mechanisms of age-related diseases, that emerge by the ecological, genetic, and ontogenetic models, the pathologic influence of the involutional model of the formation of diseases increases. A new stratum of problems, tasks, and solutions directed towards overcoming the "future diseases" per se will obviously spring up in the forthcoming period of overcoming the major diseases and prolonging the maximal lifespan of humans.

Thus, we have four different approaches to understanding the origin, prophylaxis, and treatment of the major human diseases. For example, the development of atherosclerosis due to overeating is consistent with the ecological model; in the case of familial hyperlipidaemia, it corresponds to the genetic model; impairment of the internal layer of the arteries corresponds to the accumulational (involutional) model; and age-related disturbances in fat and carbohydrate metabolism correspond to the ontogenetic model. This approach eliminates the confusion which is often observed in investigations on atherosclerosis, when some authors attribute this disease to aging, while others, to a pathologic process that is unrelated to aging. Certainly, in a real situation, the factors that relate to each of these models act jointly, and determine, in particular, an individual choice of diseases (or group of diseases).

In addition to common diseases, there may exist separate diseases for each of the four models of development that are characteristic particularly of one or the other model. Thus, the spectrum of major human diseases may alter depending on the prevalence of the model of disease formation. This will first of all relate to the accumulational model, when prolongation of the maximal lifespan will make the involutional diseases predominant. This period will start in

full measure when medicine learns to control the processes at the basis of the ontogenetic model of disease development.

F. Ludwig (1980) writes that medical treatment will remain in an infantile stage until it is able to avert the internal causes of diseases just as effectively as the external ones. He adds further that to start progressive movement away from treatment focussed on ecological causes towards treatment focussed on the human being per se means to lay the fundamentals of scientific medicine to come.

In this respect there is much to be done, but, evidently, it will first be necessary to overcome the psychological barrier to understanding what the age-related norm represents, if given this, it is considered that normal diseases also exist.

Chapter 13

What Is the Norm? or The Grand Biological Clock and the "Certificate of Health"

> The harmony of rhythm is a necessary condition for the free existence of an organism. Therefore, the idea of an age-related norm is a myth. It is not enough to feel well, it is necessary to strive to be in an ideal norm.

If the changes occurring in the organism are strictly programmed, and at the same time are subjected to fluctuations, if they are the result of the interaction of numerous internal and external factors, then the following question naturally arises: how are the influences that determine the lifespan of each individual summed up?

The organism "considers" time in a short interval, using, in principle, the same factors as Homo sapiens, who introduced the notion of an astronomical day. This count is expressed by the daily periodicity of the organism's functions, of their rhythm. Almost all the rhythms are coordinated with the alteration of day and night. However, many rhythms continue in prolonged darkness.

There are also purely internal rhythms owing to the fluctuations of the processes in each cell, tissue, and, correspondingly, physiological system. All together this

has been called a biological clock in the scientific literature. But only limited stretches of time are measured by this clock. It resembles a sand-glass that measures one cycle but does not sum up a succession of measured periods. Cycles with a greater periodicity than the 24-hour one, e.g., alteration of moon phases and seasons, are not summed up with the previous count, i.e., there is no successive recording of periods in an organism.

Nevertheless, there undoubtedly exists a peculiar calendar that reflects the total changes from the beginning of life and up to death. This calendar can reasonably be called the Grand biological clock. Like the common biological clock, it is based on the same principle of changes in the rhythm, but it possesses an important feature, i.e., the Grand biological clock does not measure the rhythm, it measures the loss of rhythm. Naturally, its mechanism is "built-in" in the hypothalamus (Fig. 8).

The clock works irregularly. It can slow down, or speed up, but it always runs in one direction, that of the gradual loss of rhythm, and the reserve of the winding decreases continually. However it is possible to measure quantitatively the spent reserve of winding in the Grand biological clock. The loads that determine the sensitivity threshold of the central hypothalamic regulator to the regulating signals

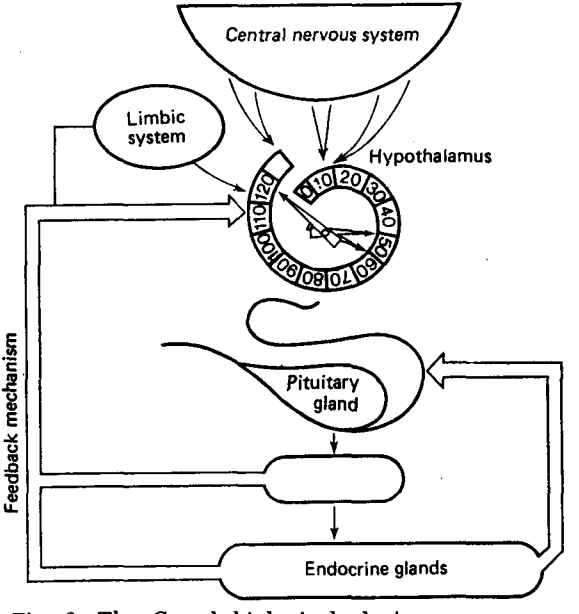

Fig. 8. The Grand biological clock.

characterize how far the Grand biological clock has gone. The more the reaction to a load has changed, the closer the finite time, or complete loss of rhythm in the functioning of the homeostat. Thus, the Grand biological clock measures the rhythm of the main homeostatic systems of the organism.

The theoretical situation can be imagined when the Grand biological clock runs so slowly that the aging process essentially

slows down. For this to happen, the functioning rhythm of the main homeostatic systems of the organism must be preserved. In turn, the latter can be attained by determining the concrete factors that cause the loss of rhythm and by finding means that prevent or reliably eliminate these disturbances.

The condition of the Grand biological clock can be judged more roughly by the changes in a series of summary indices reflecting the functioning of the main homeostats. Thus, the greater the body mass, or the cholesterol content in the blood, the greater is the risk of development of atherosclerosis, and, correspondingly, the less is the expected lifespan.

The total run of the Grand biological clock, i.e., the maximal lifespan, is determined not only by the regulatory processes of aging, but also by the local changes occurring at the cellular level as well as the activity of the systems that counteract the onset of these local changes. In turn, a certain correlation has developed during evolution between all these factors and the actual lifespan of each species in the natural habitat, which, in the final end, determines the so-called species specific limit of life.

But many factors of the environment increase the speed of the Grand biological clock. For example, deviation from the optimal food ration and an essential in-

crease in the body mass cause a disturbance in certain important rhythms in the organism and untimely changes in metabolism that are characteristic of normal diseases. As stated above, time passes faster for obese people. All this convinces one of the necessity of establishing an ideal that one should strive towards and to determine what is the norm in a continually changing organism.

This is not simple because fundamental notions are the most difficult to define. For example, what is the normal body mass for a human? A simple index is often used to calculate the body mass. This index is obtained by deducting 100 from one's height in centimetres. Thus, according to this index the normal mass at a height of 180 cm is 80 kg. But, besides the simplicity of this formula, there are absolutely no serious arguments to substantiate it.

As is known, with age humans put on mass. Taking into consideration the age-related changes in a series of physiological indices, many researchers find it necessary to establish a body mass norm for each decade of one's life. According to this approach, the body mass of a population is measured, and then the mean mass for different age groups is calculated. This averaged mass is accepted as the standard for each individual age group. In other words, a mean statistical age norm is estab-

lished, and it is assumed that an age-related change in the physiological index is normal. It is considered that only indices of body mass that substantially exceed the averaged indices for the given age group represent a deviation from the norm. Thus, the myth has come to life of the "permissiveness" of an age-related increase in body mass within certain limits, and the latter limits are calculated by the principle "to be like everybody".

But as was stated earlier, although age-related changes in the body mass occur practically in everybody, this does not mean that this phenomenon is normal. Quite the contrary, in this case it can be said that what happens to everybody is dangerous for everybody. After all, the fact is tacitly ignored that the higher the body mass, the greater the probability of death.

Thus, the growth of the organism ceases between the ages of 20 and 25. The death rate due to all the major diseases is minimal at this age. Hence, it seems most reasonable to accept the indices that are characteristic of this age as a norm, especially if the subject is not ill at this time. In essence, each human being is unique, therefore a norm is strictly individual and it is impossible to manage without averaged data.

The norm that is characteristic of everyone between the ages of 20 and 25 can be

arbitrarily designated as an ideal norm because it is the starting point from which the path towards age-related pathology begins. It is the ideal that one should strive to preserve. Any stable deviation from the individual norm at this young age is an advancement along the path to age-related pathology.

Indeed, deviation from the norm is normal in systems subordinated to the law of deviation of homeostasis because the norm is lost at one or another rate with age. This leads to the development of normal diseases. But, naturally, the rate of this loss can vary depending on many reasons. If the process occurs more intensively than on the average for the whole population in the given region, or country, then we are dealing with premature aging and the premature development of age-related diseases. Conversely, if the process of deviating from the norm is slower than usual, then we are witnessing "delayed" aging, which is characteristic of long-lived subjects. Thus, the biological age of a human may not correspond to his chronological age.

Obviously, it is impossible to measure all the conceivable physiological indices. And this is unnecessary. The majority of physiological indices are protected by the law of constancy of the internal environment and, therefore, are not subject to essential changes. It stands to reason that

accidental breakdowns that cause various diseases may occur in the organism with age. However, it is not these diseases but the ten normal diseases that characterize the process of aging. Therefore, when determining the biological age and the corresponding regular deviations from the norm, the set of indices is not so great as to be beyond consideration.

The relatively small set of indices is also determined by the fact that uniform disturbances in regulation that are stipulated by the law of deviation of homeostasis cause similar finite shifts if the aging process is occurring normally. Hence, it is possible to judge the activity of the entire system as a whole on the basis of these finite integral indices without knowing much about the plurality of intermediate stages.

Thus, for example, it is natural that the energy homeostat and the processes occurring in it are very complicated. But if the body mass that formed at the age of 20 to 25 remains stable, it is clear that the disturbances are not very great at any level of the energy system.

Considering that the law of deviation of homeostasis functions in the three basic homeostatic systems of the organism the parameters of the state of these systems at the age of 20 to 25 should be determined. The minimal number of these parameters is five:

1) body mass, or, to be more precise, the content of fat in the body (which can be calculated indirectly from the height, mass, and measurements of the thickness of the skin-folds), taking into consideration the topographic specific features in the distribution of fat;

2) level of pre-β- and β-lipoproteins and triglycerides in the blood;

3) level of cholesterol and α-cholesterol (cholesterol in high-density lipoproteins);

4) fasting blood sugar level and sugar level two hours after the intake of 100 g of glucose *;

5) arterial pressure**.

The "Certificate of Health" can be drawn up by the totality of these indices.

Indeed, the untimely development of normal diseases is practically ruled out if the initial level of the five indices listed is optimal and if their age-related dynamics are not present up to a certain time. The essentially prognostic significance of these parameters is conditioned by the fact that they reflect the state of the energy, adapta-

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* If possible, with simultaneous determination of cortisol, insulin, or C-peptide content in the blood.

** The equivalent of the ideal norm is the optimal norm, i.e., the level of physiological indices at which the incidence of diseases (the development of which is determined by the deviation from these indices) is minimal.

tional, and partially, the reproductive, homeostat. The stability of these indices at repeated examinations, e.g., once per annum, would indicate that the "Certificate of Health" is not overdue.* Conversely, changes would serve as a signal to take certain measures, including medical treatment.

We focus special attention on the fact that the "Certificate of Health" system presented here is not simply an additional system for recording certain medical indices; rather it is a reflection of a new approach to understanding the causes of development of the major diseases in humans, an approach based, in particular, on the principle of a "stable norm". It is precisely this principle, which, though lacking in all other schemes of prophylactic medical examination of the population, is decisive when assessing any system because it determines indices for medical interference. This should be fully comprehended, especially today when elaborating measures for the complete prophylactic medical examination of the population in any country. The principle of a stable and individual norm can play a tremendous role in this

* It is interesting to cite data indicating that over a period of 32 years of observation of healthy men, the initially higher level of cholesterol predetermined an earlier age-related shift of this parameter.

undertaking to prolong a happy active life for everyone.

But, when speaking about the future, it becomes necessary to learn how to determine earlier changes, i.e., at the time when the value of the final indices has not yet increased and the rhythmic functioning of the basic homeostatic systems just levels out.

Naturally, there is a "second series of tests" for each homeostatic system that makes it possible to assess more correctly the state of regulation in the system. These tests have been discussed in part in Chapters 4, 6, and 7. Certainly, the individuality of the norm demands standardization of the methods of examination. The higher the requirements for individualization, the higher the requirements are for standardization. But, this can be done and must be done because too much depends on it.

A norm is unanimous and this thesis is of more profound significance than it seems at first sight. The formation of an optimal norm in the next generation is directly dependent on the preservation of the norm in the potential parents, just as the preservation of the standard of normalcy in the entire population depends on a normal pregnancy in each particular case.

Therefore the chain of causes and consequences that determine the specifications of an ideal norm will be discussed in the next chapter.

Chapter 14

Age-Related Norm and Accelerated Development

The accelerated development is the acceleration of age-related pathology.

Human life starts from the moment of fertilization, but the fate of the future organism is to a great extent determined long before the beginning of pregnancy. We have discussed in Chapter 3 how metabolic disturbances develop in the maternal organism during pregnancy and ensure conditions for the development of the fetus and, in particular, for the increase in its cell mass.

Table 7 presents data on some shifts in metabolism during normal pregnancy. One can see that during pregnancy the glucose level in the blood increases above the norm after a glucose load, i.e., a diabetes-like condition develops. Meanwhile, the surplus glucose in the blood stimulates excessive secretion of insulin, which causes an accumulation of fat in the organism of a pregnant woman and results in an increase in the free fatty acid level in the blood. As a consequence, the utilization of free fatty acids as a source of energy increases. This,

Table 7. Metabolic Shifts in the Blood During Normal Pregnancy (after Yen, 1978)

Index	Before pregnancy	During pregnancy
Fasting blood sugar level, mmol/l	4.4±0.1	3.8±0.1
"Glucose square" (after glucose loading)	81.8±17.7	210.6±28.7
Fasting blood insulin level, mmol/l	70.3±7.9	116.2±14.4
Relation of insulin/glucose "square"	41.0±9.9	122.0±20.0
Concentration of free fatty acids, μmol/l	625±4	725±21
Triglycerides, mmol/l	0.87±0.1	2.07±0.1
Cholesterol, mmol/l	4.2±0.2	6.5±0.3
β-lipoproteins, conv. units	118±5	185±9

in the final end, increases the synthesis of triglycerides and cholesterol in the liver. All these metabolic shifts are necessary for the growth of the fetus (see Chapters 3 and 9). First and foremost, the glucose, which is not used in the maternal organism, is supplied to the fetus as the basic energy source for the latter. At the same time, if the glucose concentration in the blood of the fetus increases above what is required, then the mechanism of accelerated development comes into existence. Let's examine some details of this mechanism.

The higher the content of glucose in the

blood, the more insulin is secreted by the pancreas of the fetus. The higher the concentration of insulin in the blood, the greater the increase in the formation of fat cells, and the higher the content of fat in the latter, because both processes are stimulated by insulin. Therefore, an "obese fetus" develops in the mother's uterus and the mass of the newborn child can reach 4 kg and more. A large fetus is, in essence, an older fetus because all the energy processes run more intensively under these conditions. Hence, the mass of the fetus characterizes its biological, and not its chronological, age. R. Klimek, a Polish gynecologist, noted that an obese fetus begins to age fast before being born.

Thus, if the child's mass at birth is 4 kg or more, then accelerated development has already commenced. Moreover, the greater the child's mass at birth, the faster is the rate of fat accumulation at a later time. As a result, a powerful source of energy appears, which is spent in the process of body growth. It is characteristic in this respect that the periods of intensive growth in childhood are preceded by the accumulation of fat. Hence, the higher the mass of the fetus, the more probable is the increase in the growth rates. An increase in the linear dimensions of the body is the next element of accelerated development.

At the same time, the sooner the body

mass reaches a certain critical level, the earlier the reproductive cycle switches on. This is another specific feature of accelerated development. According to R. Frisch, an American researcher, the body mass of girls 125 years ago was 48 kg at the age of 16 years, while currently this mass is reached at the age of 12 to 12.5 years. Thus, accelerated sexual maturation commences. Certain hazards are concealed in this phenomenon.

It is currently known that women in whom the reproductive function switches on earlier later fall ill more often with breast cancer and cancer of the uterus body. At the same time, in patients ill with these types of cancer the age-related switching off of the reproductive function—menopause—starts on the average 2-2.5 years later than usual, and it is often preceded by long periods of dysfunctional uterine bleeding. This can all be explained as follows. The earlier switching on of the reproductive cycle is associated with more intensive hypothalamic shifts, and the later switching off is due to increased synthesis of female sex hormones in the adipose tissue (see Chapter 5). As a result, menopause starts at a later age but the excess female sex hormones have an excessively stimulating effect on the target tissues of the reproductive system, which contributes to the emergence of cancer (Chapter 10).

But the deterious consequences of accelerated development are not restricted to the reproductive function. The greater the body mass of the child at birth, the higher the concentration of cholesterol in the blood. Correspondingly, a trend towards an increase in this index has been observed in many countries in the recent decades. Thus, for example, Czechoslovakian researchers noted that between the years 1959 and 1962 the mean concentration of cholesterol in the blood was 144 mg% (3.62 mmol/l) in boys and 154 mg% (3.98 mmol/l) in girls that were between the ages of 3 and 6. But between the years 1970 and 1972, these measurements were 181.5 and 192.3 mg% (or 4.69 and 4.97 mmol/l), respectively. A higher level of cholesterol in the blood is a risk factor for earlier development of atherosclerosis, metabolic immunodepression, and cancer. In particular, such children demonstrate an increased incidence of leukemia, and, according to some data, children ill with diabetes mellitus are taller than healthy childen of the same age.

At the same time, the metabolic shifts that lie at the basis of accelerated development of a child reflect the higher probability of certain adverse consequences for the mother. For example, women, who gave birth to children with an excessive body mass, are themselves more likely to develop obesity or diabetes mellitus, and women

suffering from latent diabetes mellitus (or even a state of prediabetes) more often give birth to children who are overweight.

When considering the mechanism of accelerated development, it becomes clear why this phenomenon is manifested first of all in industrially developed countries with a relatively high living standard and excess consumption of food. Alongside the decrease in physical activity and the increased social stress, these factors contribute to substantial shifts in the concentration of glucose in the blood during pregnancy, which forms a mechanism of accelerated development. Thus, disturbances in metabolism during pregnancy represent a "programmed" disease because the growth of the fetus is impossible under conditions of stable homeostasis. At the same time, aggravation of the "normal disease of pregnancy" (surpassing the limits of the "normal disease" that is necessary for development of the fetus) is, in essence, the disease that results in accelerated development.

Apparently, a great role in the prevalence of accelerated development in industrially developed countries is played by the relatively greater age of the women at the time of childbirth. This is due to the necessity of receiving an education and to the specific style of life. As a result, the age-related metabolic shifts that have already accumulated in the female organism are summed up with

the metabolic shifts during pregnancy and create the mechanism of acceleration.

Thus, observations in our laboratory have shown that the skin-fold increment in the area of the iliac bone was 3.8 ± 0.8 mm in a group of pregnant women up to 21 years of age, while in a group of women aged 25 to 31 it was 8.5 ± 0.7 mm. Hence, even at the young age of 25 to 31 years, there are certain disturbances in metabolism that when summed up with the shifts characteristic of the "normal desease of a pregnant organism" cause more pronounced accumulation of fat. Meanwhile, the more mass a woman gains during pregnancy, the greater the mass of the child at birth, and so on. Therefore, the older the future mother, the greater the shift towards a fat-based energy source and the more pronounced the stress influences, the more probable is the reproduction of the acceleration mechanism in the future generations. For example, acceleration causes intensive development of age-related pathology, which is conditioned, in particular, by a shift in the metabolism towards the fat-based energy source. The presence of these specific features in a woman during the reproductive period increases the probability of giving birth to a large child, i.e., the offspring may repeat with greater probability the fate of the accelerated parent. In other words, not every accelerated per-

son descends from another one, but acceleration is more probable if the mother experienced accelerated development. Hence, if the age of a woman who is giving birth for the first time is increased due to various factors of civilization, if the factors of civilization increase obesity among the young generation, if stress situations are less controlled, if, in short, conditions are created that exacerbate the "normal disease of a pregnant organism", then the frequency of accelerated development should increase.

This illustrates how the chain of the acceleration mechanism closes, which in the final end causes an accumulation of accelerated individuals in the population. The example presented above shows how the principle of uncertainty, which reveals itself in the diversity of variable factors of the external environment, in interaction with the principle of determinism, to which the mechanism of development of the organism is subordinated, creates a situation wherein accelerated development is directly transformed into acceleration of aging and the development of age-related diseases. Certainly, an increase in the number of accelerated individuals in a region under these conditions is not an index of changes in heredity under the influence of external factors; rather it is the realization of the choice of extreme variants of development

in the normal distribution of the specific genetic features of the species.

From this point of view, the principle of the ideal norm (Chapter 13) may be unfounded in certain populations because the norm may already be lost by the end of the organism's growth. Therefore, alongside the notion of an ideal norm, the so-called optimal norm is very important. It is the value of the physiological parameters at which there is minimal mortality (incidence of disease) due to diseases associated with a disturbance in these parameters. Hence, the optimal norm is useful to assess the condition of people of any age.

It should be emphasized that there are certain arguments that make it possible for the author to assume the existence of a second mechanism of accelerated development that operates not in ontogenesis, i.e., during the life history of one generation, but in phylogenesis, i.e., over the period of several generations. The second type of accelerated development and acceleration of age-related pathology arises in regions and countries with a low living standard and high infant mortality due to shortage of food resources, infectious diseases, and poor medical services, i.e., in countries with a low mean lifespan due to the high death rate of individuals as a result of external causes. The mechanism of the second type of acceleration can be presented

as follows if considering the comments to Table 5 in Chapter 11. If infant mortality is high, then women in whom the capacity for childbirth matures at an earlier age have the advantage, as a result of which these women manage to give birth to a greater number of children. But, as we determined above, early sexual maturation is a typical indication of accelerated development, which, in the final end, causes a decrease in the lifespan owing to acceleration of the ontogenetic mechanism of the major diseases. Gradually, the descendants of women with an accelerated type of sexual maturation and, consequently, with an inherited tendency for accelerated development begin to prevail in the region. Therefore, in countries with high mortality from external (ecological) adverse factors the following demographic situation is frequently observed: early sexual maturation, predominance of young, physically well-developed individuals, high birth-rate, rapid aging, and short lifespan even in the presence of sufficiently favourable living conditions. If there existed a method for determining the species specific (maximal) lifespan in such populations, then undoubtedly a decrease in the lifespan would be observed.

It should be noted that accelerated development of the organism is more dangerous for males owing to the specific features

of the male organism and his role in reproduction. It is essential that this problem be addressed in the next chapter because, owing to the greater knowledge about certain features of the female neuro-endocrine system and a greater frequency of certain endocrine diseases in women than in men, more examples concerning the female organism have been given in this book. This may have created the false impression that the male organism is less vulnerable to age-related diseases.

Chapter 15

The Female and the Male: Four and Three Stages of Life

The different roles of the female and male organisms in reproduction have determined that females live longer than males at all the levels of the evolutionary tree of life. The means supporting these differences vary at different levels of evolution of the animal kingdom. Male mammals have neither a stage of stabilization, nor a mechanism for the age-related switching-off of the reproductive function. The absence of advantages that are associated with stabilization is the price that the male organism pays for the absence of the male climacteric.

"Rejuvenation" of the development of age-related pathology has been most vividly manifested in males during the last decades. This is partly due to the influence of certain unfavourable factors of civilization. But, the following question naturally arises: why are these factors more dangerous for men than for women?

The same situation exists in the animal kingdom, i.e., the lifespan of the male is shorter than that of the female. This points to the decisive significance of biological factors in the formation of the mechanism of aging and natural death. Therefore, we shall discuss some accessible aspects of the biological difference between the sexes and try to determine how this difference in-

fluences the rate of development of age-related diseases.

It is known that both sides participate equally in reproduction. But this equality relates to the transmission of genetic information and not to the functioning of the reproductive system.

The possibility of fertilization is limited by the female organism owing to the fact that the ova are cyclicly (as is known, approximately once a month) supplied for fertilization. This process demands the accurate and rhythmic operation of the reproductive homeostat; therefore, its central hypothalamic regulator must be highly sensitive to the female sex hormones that participate in the functioning of the feedback mechanism and maintain the strictly rhythmic activity of the system. The second requirement consists in creating optimal conditions in the organism for procreation.

The reproductive homeostat of the male organism performs quite a different function in reproduction. It must ensure the continuous possibility of participating in reproduction in order to overcome the limits set by the cyclic appearance of the female ova. This is achieved by the continuous maturation of male sex cells. Therefore, the male organism is able to participate in conjugal union with many individuals whose readiness for reproduction occurs at different times.

The permanent type of functioning of the male reproductive system is provided for by elevation in the sensitivity threshold of the hypothalamic "sex centre" to inhibition by the sex hormone testosterone with increasing age. This creates deviation of reproductive homeostasis that increases the power of the system. It is interesting to note that the high level of testosterone in the blood that corresponds to the level in young men is found sometimes in 80- and 90-year-old men. Thus, an increase in the power of the reproductive homeostat maintains the necessary potency in the male organism.

In accordance with these different requirements, the influence of the female and male sex hormones on the hypothalamus and on metabolism is different. The male sex hormone plays an important role in the formation of the sexual characteristics of the hypothalamus itself. An animal organism begins life with a "sexless" sex centre which in both males and females preserves the ability to function as a female, i.e., the rhythmic type of functioning. The "sex centre" in the male organism becomes a truly male one under the influence of the male sex hormone produced by the immature animal and begins to function in the permanent, nonrhythmic mode.

This loss of rhythm is equivalent in a certain sense to early aging in the male

organism as compared to the female. Thus, it has been experimentally established in animals that if testosterone is injected into an immature female during the first days of the animal's life, the hypothalamus will function throughout the animal's entire lifetime according to the male pattern, i.e., in a nonrhythmic mode. In maturity the incidence of tumours increases in these animals and this reflects accelerated aging.

In accordance with the biological role, aging occurs quite differently in the female and male reproductive homeostat. In the female, the rhythmic activity of the homeostat continues from the age of 12 to almost 50. Cessation of the reproductive function (menopause) occurs when the elevation of the hypothalamic threshold disturbs the mechanism of self-regulation (Chapter 5). This automatically limits reproduction during the period when the accumulation of age-related changes causes deterioration in the condition of the female organism and increases the various types of risk that are linked with pregnancy and the age-related accumulation of mutations that are dangerous for the progeny.

The male organism is not directly taxed by procreation, and only performs the male part of the transmission of genetic information. Hence, there is no climacteric in the male organism, i.e., no mechanism of age-related cessation of reproduction. How-

ever, there is a gradual decrease in potency in the course of aging, which limits the ability to transmit genetic information. The decrease in potency with increasing age is strongly associated with a deterioration in the general condition of the organism, which is, first and foremost, a result of the lack of a stabilization phase. The latter phase is induced in the female organism by the female sex hormones. What are the specific characteristics of this phase?

In childhood the level of free fatty acids in the blood in both the female and male organism is much higher than in young adults. The level of cholesterol in the blood of children is also higher than at the age of 20 when body growth ceases.

This shift to fat-based metabolism is necessary to fulfill the growth requirements, and, in essence, it is a deviation of homeostasis, which is an obligatory condition of development. But according to the character of metabolic disturbances, it corresponds to a "normal disease", to a state of prediabetes, i.e., to metabolic shifts characteristic of aging. In light of this interpretation, the following old observation becomes clearer: the deposition of fat and cholesterol in the aorta in early childhood creates islands of future atherosclerosis (though they are temporarily resolved at a certain age). In truth, "the old are like the young". Therefore, the author calls

this stage of growth as the stage of pre-prediabetes.

The switching-on of reproduction in the female organism stabilizes metabolism. This is manifested by the fact that the level of the free fatty acids drops during sexual maturation, reaching a minimum at the age of 16. It should be noted here that the level of free fatty acids in the blood of children whose sexual development is more accelerated reaches values that are characteristic of adults between the ages of 4 and 7.

Studies have shown that female sex hormones prevent growth hormone from mobilizing free fatty acids from depot sites and perhaps therefore possess the ability to reduce the cholesterol content in the blood. Women between 30 and 39 years of age do not demonstrate an increase in blood insulin or sugar levels, which corresponds to the stage of stabilization. But the sex hormones in the male organism do not give rise to the stage of stabilization; therefore, with an increase in age the concentration of insulin in men increases more than in women. On the whole, between the ages of 21 and 49 the postprandial increase in the insulin concentration in men is 3 times greater than in women.

As we remember, insulin is the major risk factor in the development of atherosclerosis. It is possible that this is the reason

why atherosclerosis develops almost 10 years later in women than in men. This is a significant difference in the times of onset of "diseases of compensation" and may be the reason for the 10-year advantage in life-span that women have. A series of major physiological indices remain practically unaltered in women during the stage of stabilization.

However, the reproductive cycle switches off in women of a certain age in accordance with the law of deviation of homeostasis. Then the stage of stabilization is replaced by another stage similar to the one in childhood except that "normal diseases" of aging form intensively at this new stage of prediabetes in accordance with the program of development. Correspondingly, removing the ovaries from a woman before she has reached the age of 40 leads to an increased rate in the development of atherosclerosis. In other words, the sexual advantages associated with the stage of stabilization are lost.

By the age of 70 the age-related increase in insulin is similar in men and women. This demonstrates the end of slowing down of the Grand biological clock, which was attained during the phase of stabilization in women, and reflects the identical nature of the programs of development in both sexes. In accordance, the indices of mortality from "normal diseases" level out in men and women by the age of 70.

Nature, however, has presented the human being with one more stage: the stage of involution. Thus, data indicate that the mean level of cholesterol in the blood of men and women after 60-70 years of age is slightly lower than in the previous stage of prediabetes. It is assumed that this decrease is associated with increased mortality (in particular, from atherosclerosis) in people with a high level of cholesterol. A real decrease in hypothalamic activity may also occur with age. Thus, climacteric neurosis frequently rages for 5 to 10 years and then disappears on its own. Apparently, the accumulation of shifts on the cellular and tissue levels and, in particular, in the hypothalamus, as in any other tissue, evens out the specific changes in this system over the course of time.

The storm of regulatory disturbances, which induce diseases, calms down a little. A relatively favourable stage of involution, or aging, starts, and the rate of development of age-related diseases decreases. If, by this time, the major diseases have not made an appearance, then those who have reached the age of 70 have a statistical probability of living an additional 15 years or more. In this case, the body mass often drops.

Statistical data indicate that fewer people die of certain types of cancer during the stage of involution and this is reflected

equally in regions with a high mortality rate from this disease (Finland) and in those with a low rate (Portugal).

Hence in principle, the type of changes in the energy and reproductive homeostat in female and male organisms is the same. However, the specific features of the female organism that are associated with the switching-on of the reproductive cycle induce the stage of stabilization. Thus, if the life of a male conditionally consists of three periods, i.e., growth and maturation (pre-prediabetes), maturity (or prediabetes, when age-related pathology intensively develops), and, finally, the period of involution (when the rate of formation of age-related pathology slightly retards), then a female lives through four stages, i.e., pre-prediabetes is replaced by the period of stabilization, which creates optimal conditions in the organism for reproduction, and only then do the stages of prediabetes and involution commence.

Hence, the absence of the stage of stabilization in the life cycle of the male organism probably predetermines the male's shorter on-the-average lifespan. However, the stage of involution again evens out the potentialities of the sexes, and old age discloses unexpected sides in the perception of reality for those who have reached it.

Chapter 16

To Treat or Not to Treat? How to Retard Aging?

> We use life's blessings every day, we age as the days pass, therefore we must counteract aging daily.

It is clear to the reader that these questions are purely rhetorical: they are simply to focus attention on the issue.

According to the ontogenetic model of the major human diseases, their mechanism is linked with the regulatory and, partially, the metabolic processes of aging. Therefore, in order to slow down the development of these diseases of middle and old age, it is necessary to learn to retard aging. This conclusion is a direct consequence of the ontogenetic model of medicine, and clinical observations as well as statistical data empirically correspond to it. In particular, L.A. Gavrilov and co-workers (1978, 1983), who worked out the so-called life tables for Sweden for the period from 1910 to 1978, found that the substantial decrease in mortality observed during this golden age of medicine occurred on account of the decreased mortality from diseases that were not linked with aging. Thus, one may conclude that new ways must be

found for the prophylaxis and treatment of the major human diseases via ontogenetic mechanisms.

Meanwhile, there is a psychological barrier in modern medicine that limits comprehension of the role that should be played by gerontology in clinical medicine as a whole and in the fight against the major noninfectious diseases in particular. This barrier is conditioned partially by the belief that the aging processes are very complicated and elude complete understanding at the current stage. It is also widely believed that aging, as a physiological process, has *nothing in common with* the onset of the major diseases; rather, it only forms the background against which they develop. In addition, it is assumed that because of the complexity of the aging process it is impossible to create a sufficiently practical system of antiaging treatment.

Finally, serious scientists are perplexed by some hasty prognoses made by researchers who are not specialists in the field but, nevertheless, assert that the secret of immortality will be revealed in the nearest future. On this basis, promising recommendations are easily given but they are simplifications of conclusions derived from both orthodox and folk medicine. What is more, from time to time extremists appear who advocate radical measures; some of

them prohibit the consumption of animal protein, animal fat, vegetable fat, or carbohydrates, or they suggest a "zero diet", i.e., long-term periodic starvation. Others find deliverance from the burden of age-related diseases in maximum activity, still others in peace of mind, or mental relaxation. Those who recommend such diets usually pass through two peaks of popularity: first because of the extreme character of their recommendations; and then, because of the harm caused by these extremes. Strangely enough it is usually forgotten that none of these heralds of such fads ever introduce anything new except the heat of their conviction. This is all akin to superstitions and prejudices while only knowledge is power. Nevertheless, many of these enthusiasts, owing to their persistence and the fact that, on the whole, their recommendations echo those of orthodox medicine ("don't overeat, don't smoke, don't worry, and move more") achieve certain positive results. Therefore, let's first discuss these recommendations from the scientific point of view.

A surplus of animal protein and cholesterol in the food accelerates the development of atherosclerosis and some types of tumours (e.g., cancer of the large intestine and breast cancer); a surplus of saturated (animal) fat contributes to the onset of atherosclerosis, and a surplus of vegetable fat, to a

decrease in immunity. In turn, decreased immunity leads to the development of atherosclerosis and cancer. But if all these components are eliminated from the diet and there is a surplus of carbohydrates, obesity commences. It is the disease of all diseases: type II diabetes mellitus, metabolic immunodepression, atherosclerosis, and cancer are all associated with it. Finally, extreme dietary restriction, especially in protein, also causes a decrease in immunity in addition to an increased risk of mental depression, which also contributes to the development of the major diseases.

Since the entire energy base of the diet is made up of carbohydrates, proteins, and fats, both saturated and unsaturated (only four components), it is clear that a surplus (just as a shortage) of any one is dangerous for one's health. Imagine that a person is inside a square. Each side of this square can be the source from which carbohydrates, proteins, and saturated and unsaturated fats are freely derived. But this freedom limits the lifespan.

It may seem that in this description the danger is exaggerated. This false impression arises because for many millenia humans have battled with a shortage of food resources. This problem is still acute in many countries today. However, in many cases it is not a shortage in food but its surplus that is the factor causing un-

timely aging and diseases that are linked with it.

Let's discuss the recent experiments carried out by Robert Good, a well-known American immunologist.

Certain strains of mice suffer from the same diseases as contemporary human beings: cancer, arteriosclerosis, myocardial infarction, kidney disease and hypertension, obesity, diabetes mellitus, auto-immune diseases, untimely atrophy of the thymus, and a decrease in immunity. Naturally, such strains of mice have shorter lifespans than do ordinary mice. When the content of protein was reduced in the diet of these animals, there was a decrease in the incidence of auto-immune diseases. A decrease in the caloric value of the diet, which was nutritionally balanced, produced a still greater decrease. The incidence of diseases decreased so drastically in the animals that their lifespan increased to normal values.

Other experiments showed that in strains of mice characterized by high longevity a decrease in the food ration, as compared to what they picked themselves, also increased the lifespan by 25%.*

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* A large number of experiments carried out since the 1940s have demonstrated that, by restricting the caloric value of the diet of rodents, the duration of sexual maturation and, correspondingly, the maximal lifespan are increased (see the relationship between these processes in Chap-

Thus, it is possible that humans can also avoid many troubles, or, at least, choose the least one from the lot by ingesting only the required amount of food. In this regard the ancient Greeks first made the observation that a sense of proportion guaranteed a healthy body and spirit.

Let's try to find this sense of proportion though it is more difficult today than in ancient times because civilization has created new foods (e.g., sugar), while other foods such as common vegetables have been devalued in the eyes of modern humans.

The following example clearly shows the result of surplus sugar in the diet. If a middle-aged adult eats a large quantity of sweet food (equivalent to 50 g of sugar),

ter 11). It has been suggested that in the case of primates and, especially, humans, this interaction may be less significant because the period of maturation is already sufficiently long. However, the influence of optimal nutrition is realized by many mechanisms. In particular, its favourable effect has been demonstrated in animals when dietary restriction is begun at the age of one year, which corresponds to the late period of maturation in humans. Finally, statistics derived from large populations demonstrated that in humans a change in "life-style", including a decrease in the consumption of animal protein and fats, an increase in the content of vegetable food in the diet, reduced smoking, increased physical activity, and better treatment of hypertension reduced mortality due to ischaemic heart disease in middle-aged adults by more than 30% in the period between 1950 and 1979.

the concentration of insulin in the blood two hours later increases from two to three times. In addition, experiments have demonstrated that 30 minutes later these increments of insulin increased the synthesis of cholesterol in the aorta twofold.

It should also be remembered that the evolution of humans as a species is infinitely slow, while the evolution of our diet is disproportionately fast. Vegetable food has been a basic part of the diet for millenia, but today it is impossible to return to it because the change in the life-style and in the pace of life, and the changes in the digestive organs that occurred over the course of these years demand the additional inclusion of a certain quantity of animal protein, and vegetable and animal fat. For example, animal fat contains vitamin D, which is indispensable for humans. Our closest relatives—the monkeys—who also require it, receive it from other sources. Living in the trees of the tropics, they are subjected to intense ultra-violet radiation, under the effect of which provitamin D is produced from the initial food source. This method is impossible for us today. It is also impossible for us to eat a kilogram of vegetables and then to fall asleep and digest it for a long time in order to obtain the required quantity of protein that forms the foundation of our body. In general, vegetables (except for soya) contain a

relatively small quantity of the required amino acids, which are the building blocks of protein.

Nevertheless, the main part of the diet should consist of vegetables. Moreover, a certain quantity of rough plant food that contains so-called nondigestible plant fibre, i.e., cellulose, pectin, hemicellulose, lignin, etc.,* should also be consumed. These foods reduce the incidence of cancer of the large intestine, retard the development of atherosclerosis, and decrease the incidence of cholelithiasis and even varicosis.

This has all been well tested, and for this reason wide-scale prophylactic measures are based on these conclusions. Thus, it has been shown that by switching to a diet with a lower content of saturated fat, cholesterol, sugar and common salt and a higher content of starch and undigested vegetable fibre, a decrease in the incidence of early myocardial infarction, stroke, hypertension, diabetes mellitus, and cancer results. It has been established that those

* A large amount of plant fibre is contained in any variety of cabbage, apples, spinach, rutabaga, and many other vegetables and fruits. The protective influence of vegetable fibre is manifested most clearly in the presence of a large quantity of fat in the diet. According to a series of data, daily diet that contains 35 g of vegetable fibre decreases the mortality from cancer threefold as compared to a diet with a low content of vegetable fibre.

who adhere to this kind of diet live 8 years longer on the average than those who don't. This "gain" will seem still greater if it is considered that "losers" fall ill with serious diseases not for eight but for many more years.

Table 8 presents a balanced diet that contains about 1800 calories.

This diet is based on a low content of cholesterol, limited amount of saturated (solid) fat, a slightly larger amount of unsaturated (fluid) fat, as well as a large amount of roughage that contains a sufficiently large quantity of vegetable fibre. Four, or even five, meals should be consumed in one day because only a relatively small quantity of energy substances can be "burned" at one time. For this reason, if a person eats only once or twice a day, obesity can begin to develop even in the absence of a dietary surplus.*

* After obesity has developed, its stabilization is attained with a smaller quantity of food than that required in the active phase of fat accumulation: this is because in obese people thermogenesis does not increase with food intake. When a restricted diet is indicated, e.g., in atherosclerosis, cheese, whole milk, ice cream and cream must be excluded but the diet should include more vegetable oil. It is believed that it is better to break one's diet once in two weeks than to permit slight deviations daily. Nevertheless, one should remember that one's appetite increases after overeating. Alcohol is most dangerous when there is an elevated level of triglycerides in the blood.

Table 8. Composition of Foods in Terms of Carbohydrates (C), Saturated Fatty Acids (SFA),. Unsaturated Fatty Acids (UFA), Cholesterol (Ch), Carbohydrates and Unsaturated Fatty Acids (C+UFA)

Food products	Composition				
	C	SFA	UFA	Ch	C + UFA
Lean meat or fish	150	150	150-200	100	200
Curds:					
semi-fat	150	—	—	—	200
skimmed	—	200	150-200	200	—
Milk (kefir, sour clotted milk)	500	500	500	500	500
Cheese	25 (50%)	25 (30%)	25 (30%)	15 (30%)	15 (30%)
Egg	1	—	—	—	—
Brown bread	75	75	100	100	100
White bread	—	75	100	100	—
Butter	30	10	25	10	15
Margarine	10	10	—	—	10
Vegetable oil	20	20	10	15	20
Vegetables (except potatoes)	400	300	400	400	400
Potatoes	—	100	100	100	—

Table 8 (concluded)

Food products	Composition				
	C	SFA	UFA	Ch	C + UFA
Fruits, berries (except grapes, bananas)	400	300	400	400	400
Buckwheat, oatmeal	25	40	40	40	25
Sugar	—	20	20	20	—
Sour cream	50	—	—	—	25
Vitamins	ABCPPE	A+D	A+D	ABCD PPE	ABCD PPE
Kcal	1800	1800	1800	1800	1750
Carbohydrates, g	125	200	225	230	135
Fats, g	110	75	58	60	80
Protein, g	80	82	85	77	87
Cholesterol, mg*	510	260	350	200	350

* In patients predisposed to atherosclerosis, 250 mg/day of cholesterol are permissible.

Of course the effectiveness of applying the same standard diet to everyone is limited for several reasons. A standard diet is based on common principles, but frequently an individual approach is required. For example, if the content of cholesterol in the blood is elevated, the consumption of cholesterol, which is available in meat, eggs, and butter (Ch-diet),* must be strictly limited. If the content of blood triglycerides is elevated, the content of carbohydrates in the diet (C-diet) must be limited and body weight lowered. If the content of cholesterol and triglycerides is elevated, both must be limited (C + SFA-diet) and vegetable fat must be increased in the diet. In the final analysis, a diet ensuring that the organism maximally approaches the ideal norm is the one that should be followed. To this point, long-lived subjects show an elevated level of high-density lipoproteins in the blood (HDL, or α-cholesterol), while the concentration of low-density and very low-

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* Dietary cholesterol plays an important role in the organism when there is an increased quantity of cholesterol in the blood. An excess consumption of cholesterol (1000 mg/day) can elevate its content in the blood by 30 to 60% within 3 to 4 weeks (the content of cholesterol in one egg yolk is about 240 mg; in 100 g of butter, 220 mg; in 100 g of cream, 137 mg; in 100 g of meat, about 60 mg; in 100 g of milk, about 13 mg; and in 100 g of cheese, (30-40%) about 90 mg).

density lipoproteins (LDL and VLDL) is decreased.*

Let's define more accurately what is meant by the statement that obesity is the disease of diseases. In a strict sense obesity commences when the quantity of fat exceeds the ideal norm by 4.5 to 5 kg. Therefore, the body mass should be maintained at the level reached by a healthy person at the age of 20 to 25. This requirement is not extreme because muscle and bone tissue decreases with age: thus, even if the body mass remains the same between the ages of 25 and 70, the fat content increases by approximately 30% (see Chapter 6). If it is born in mind that a 25-year-old person who weighs 70 kg has about 15 kg of fat,

* Currently, the concept of an optimal concentration of cholesterol in the blood ranging between 174 and 212 mg% (4.5-5.5 mmol/l), at which the incidence of myocardial ischemia is minor (as compared to populations with a high cholesterol content in the blood), has become widespread. It should be noted that in middle age the optimal level of cholesterol, which in many aspects corresponds to the ideal norm (see Chapter 13), can be achieved only through observance of a strict diet, or as a result of special treatment. The decrease in blood cholesterol levels through dietary manipulation has nothing in common with the genetically predetermined condition characterized by low blood cholesterol levels and its high excretion by the intestines: the latter condition predisposes to the development of polypi and increases the risk of cancer of the large intestine.

then this "inconspicuous" addition is equal to the 4.5 kg that should be avoided.

Therefore, it is necessary to ensure not only an ideal body mass, but also a certain degree of physical activity that retards the substitution of muscular tissue by adipose tissue. A high degree of physical activity also contributes to the establishment of a favourable ratio of HDL to LDL and VLDL (see below).

The standard diet can also be ineffective because it does not sufficiently consider certain factors. This problem can be explained in various ways but let's restrict ourselves to the following cases. An individual diet should be conditioned not only by an ideal individual norm, but also by factors reflecting the constitutional and family predisposition to various diseases. For example, it has been established that if breast cancer has occurred among relatives, then attention must be paid to preventing obesity, and if this concerns girls who have not yet reached sexual maturity, then intensive physical activity approaching that reached in professional ballet classes is necessary.

If cancer of the gastrointestinal tract has been registered among relatives, the diet should contain more vegetables (vegetable fibres) and vitamins A, E, and C. In general, sufficient data currently exist in favour of increasing the prophylactic dose

of some vitamins in order to achieve an antitumoral effect. Vitamin A contributes to the correct maturation of the epithelium cells, especially of the gastrointestinal tract and lungs; vitamin E protects the cells against the damaging effect of the breakdown products of fat; vitamin C has the same effect in addition to many others, including an antistress effect. In the stomach, the latter vitamin also inhibits the formation of chemical carcinogens (nitrosamines) from proteins and nitrous salts that are added to many foods as preservatives.* Vitamins B_6 and B_3 (nicotinic acid) increase the content of serotonin in the brain, which is one of the basic neurotransmitters that improves one's mood and metabolism. As we currently know, one's mood greatly depends on one's diet, or, to be more precise, on the sufficient supply of tryptophan—an amino acid—to the brain. This is ensured by increasing the content

* Vitamins A, E, and C have quite diverse functions that relate significantly to antioxidant systems. These systems counteract the damaging influence of free radicals, which are associated with many elements of metabolic aging (see Chapter 11). In particular, vitamin E counteracts damage to the membranes and DNA; vitamin A (β-carotene) has an antitumoral effect in regard to viral, chemical and radiation carcinogenesis, and stimulates immunity. However, optimal doses for vitamins as well as for selenium, zinc, and methionine, which possess the same effects, have not yet been established.

of protein or carbohydrate in the diet, which supports the entry of this amino acid into the brain.

However, all these problems have not been sufficiently studied. Therefore, when something paradoxical is encountered, confusion results among the ranks of some gullible researchers who deny all the knowledge that was obtained with great difficulty about a rational diet. For example it has been found that Eskimos, who consume a large amount of meat and, correspondingly, cholesterol, rarely suffer from atherosclerosis and myocardial infarction, although the connection between cholesterol and these diseases has been quite definitely established. It turns out that a certain fatty acid, which possesses an antisclerotic effect, circulates at a high concentration in the blood of Eskimos, and the rate of rendering the fatty acids harmless is increased.*

These two basic factors, i.e., the specific individual features inherent to each person, which are not taken into consideration in the general approach to the diet, and an

* The incidence of myocardial infarction, diabetes mellitus, and auto-immune diseases is reduced in Eskimos and this is associated with the specific genetic features that arise in a separate human population that has been isolated from others for almost 5000 years. Longevity, observed among some nations (e.g., in the Caucasus), is also, apparently, associated not so much with the lifestyle as with the genetic (and biochemical) factors.

as yet insufficient amount of data, result in the fact that the standard diet is not a means that can help in all cases. But one should not forget about the additional years of healthy life that are provided by a modern diet, or, to be more precise, by a rational life-style.

It should also be remembered that the standard diet is intended mainly to decrease the accumulation and utilization of fatty acids as fuel. But not everything that is useful for preserving one's health is determined by rational nutrition. The life-style is just as important, because, as was stated by the ancient Greeks, we eat to live, but we do not live to eat.

An acrimonious person, who gets irritated with or without good reason, may experience greater shifts in metabolism than a good-natured gourmet. And one who finds satisfaction in the rational control of one's requirements benefits the most. Once, a philosopher who was visiting a friend whom he found living in luxury said, "How many things there are that I don't need".

But one who has been able to follow this principle also requires satisfaction in work. For this reason one should not place so many hopes on yoga: it is not only a system of sensible exercises; it is also a philosophy directed at the study of one's self, and this personal position is impossible in modern society. On the other hand, sound auto-

genic training, whose purpose is to teach one to control one's emotions, is undoubtedly useful if we recall the role of stress in the development of diseases.

In addition to diet and mental hygiene, physical activity, with emphasis on quality rather than intensity, is the third requirement for counteracting age-related diseases. There is a "limiting link" in metabolism that cannot be overcome by physical activity alone, or by a rational diet alone: both must be engaged in simultaneously.

One must engage in rather intense physical activity that ideally corresponds to the training regimen of middle- and long-distance runners: for this reason it is rarely applied in everyday life. But many modern systems of "physical training for everyone", which are based on walking or running, are quite effective. It is amazing that the metabolic index in a 70-year-old man can be improved in four to five weeks: this has been demonstrated by a series of well-controlled studies.

At the same time, physical activity is something that must be engaged in daily. However, "running from infarction" should be sanctioned by an experienced doctor. "Running from infarction" is, apparently, also equivalent to "running from cancer" because the content of α-cholesterol (high-density lipoproteins) increases during intense physical activity: this is a factor that

plays a protective role in regard to metabolic immunodepression, atherosclerosis, and, possibly, cancer.

Finally, the struggle with so-called harmful habits, including passivity of thinking, must also be addressed. One of the most adverse effects of aging on the organism is due to one's idea of aging. Concepts about aging from the last century continue to haunt us in this respect. It is high time to recognize that social progress has not only extended the human lifespan, it has also called for a reconsideration of what the chronology of age and old age means.

In the past century a writer could write, "An elderly man of fifty entered the room." In the twentieth century even an inexperienced young writer would hardly find it possible to write anything like that. However, in reality people who are between the ages of fifty and sixty frequently consider themselves to be old. This must be reconsidered! The extension of the active period of life should be supported by a change in the psychological assessment of the "age labels": this in itself will serve to extend the lifespan.*

* The formation of one's attitude toward retirement also belongs in this category. This process is more harmful and threatened more by the development of diseases in men than in women, especially after the second year of retirement. Thus, it is necessary to psychologically prepare

As far as harmful habits are concerned, one very nice lady once said to this author: "You doctors are mistaken when you try to frighten us by saying that smoking is dangerous and even life threatening. People are brave by nature; therefore it is better to say that smoking ruins the colour of your face, or makes you less attractive."

Nevertheless, there is something to fear in smoking. According to 1980 statistics from France, if the risk of cancer in nonsmokers and nondrinkers is taken to be equal to unity, then in drinkers who do not smoke, it is 1.23; in smokers who do not drink, it is 1.53; and in smokers who do drink, it reaches 5.71.

Almost 90% of the cases of cancer of the lungs is attributed to smoking. (Certainly, it does not develop in every smoker. A high level of cholesterol in the blood intensifies the harmful effect of smoking.) Smoking also increases the incidence of cancer of the larynx, pharynx, oesophagus, urinary bladder, and liver. A nonsmoker inhales about 2.3 mg of ash per hour when staying in a room with a smoking person (this is called passive smoking).

Many people believe that smoking helps to lose one's weight. Frequently, this

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oneself for this period at the proper time by, first of all, determining the possible types of work (or occupation) that one could engage in during retirement.

is really the case, but the method itself is faulty because nicotine intensifies the utilization of fat as a fuel but does not prevent the accumulation of fat, i.e., it has the same effect as aging, increasing the "turnover" of fat with all the ensuing consequences. Excessive coffee and tea render a similar effect on the organism, though the fat-mobilizing factor in this case is caffeine.

According to contemporary data, coffee contains a series of carcinogens and mutagens (agents that induce mutations). There are some preliminary data, though not yet confirmed, that indicate that the incidence of cancer of the ovaries, urinary bladder, pancreas, and large intestine increases in people who drink large quantities of coffee.

Smoking, or the act of smoking, however, calms down many people and this aspect of the problem needs to be seriously studied (with consideration of the role of morphine-like hormones that partially form in the brain from the fat-mobilizing hormones of the pituitary gland).

Alcohol presents a more serious problem. Apparently, ethyl alcohol stimulates the formation of similar hormonal derivatives in the brain, which exert a peculiar effect on the nervous system. This is the first hazard because alcoholism develops in some people who are genetically predisposed to an increased formation of these hormones. Alcohol also contributes to the onset of

cancer. There is a greater susceptibility to cancer of the oral cavity, oesophagus, stomach, larynx, and less of the liver. Alcohol also reduces sexual potency in men. It can cause mental and physical disturbances in the development of the fetus during pregnancy. It contributes to the development of hypertension in many people.

The author hopes the reader will not be surprised by the fact that even excess sunlight (e.g., in the South) can be harmful because illumination intensifies hypothalamic activity. A very obvious case is incubator chickens, which are "accelerates". Excess sunlight accelerates aging, and increases the incidence of cancer of the skin and melanoma (especially in fair-haired people).

To the point, the problem of acceleration precisely helps to explain why one cannot arbitrarily choose a certain age, e.g., 40-45 years, as the time to start prophylactic measures. In reality a full cycle of prophylactic measures, beginning with childhood, and paying special attention to the period of pregnancy and other periods must be developed. And what is more, everything that happens during pregnancy greatly depends on the state of the female organism prior to the onset of pregnancy, i.e., there is a closed cycle of causes and consequences, consequences and causes, and the

entire cycle should be the object of medical observation.

It would be incorrect, however, to state that at a certain age it is too late to carry out treatment: aging is a disease of regulation and, therefore, many aspects of it can be subjected to treatment.

The measures recommended by modern medicine to prevent accelerated aging and the diseases linked with it are directed mainly at preventing the surplus accumulation of fat and its excessive utilization as fuel. This is the role of the campaign against overeating, insufficient physical activity, stress, and overconsumption of coffee, nicotine, and other stimulants of fat mobilization.

Diet can limit the defects caused by disturbances in regulation but it is unable to eliminate them completely. For this reason, it is extremely important to elaborate a theory that would determine the search for new ways and means of action.

In essence, a lot could be attained in the light of the concept considered if it were possible to ensure the use of preparations that would act only in certain ways: 1) raise the sensitivity of the hypothalamus to regulating signals; 2) decrease the production of insulin and of the main stress hormone, cortisol; 3) increase the production of such hormones as etiocholanolone, dehydroepiandrosterone, and androsterone by the adre-

nal cortex; 4) decrease the cholesterol content in the cell membranes, and 5) suppress the appetite by restoring the level of neuromediators in the hypothalamus. It is no joke that in the latter case everyone would gain (we really all burn down in the flame of our own fat). Society as a whole would also benefit because the food requirements would decrease by about one-third, and their production would be simplified.

All that has been stated above can be illustrated by several examples.

The experiments of R. Good and co-workers where a food ration for particular strains of mice was reduced from 16 to 10 kilocalories per day were already mentioned. The incidence of cancer decreased and the lifespan increased.

Similar strains of mice were used in experiments at the laboratory of endocrinology of the Scientific Research Institute of Oncology in Leningrad. The initial state of the animals in both laboratories was practically the same. The maximal lifespan of the mice in Good's laboratory was 600 days, while in our laboratory it was 641. While setting no restrictions on the food ration, and by only administering the antidiabetic preparation phenphormin, we were able to extend the average lifespan from 450 ± 19 days to 555 ± 32 days, i.e., by 25%. The incidence of cancer decreased from 80% to 20%, i.e., fourfold (Fig. 9).

Phenytoin (an anticonvulsive drug), which possesses the ability to reduce the production of insulin and cortisol, also extended the lifespan of the animals and reduced the incidence of cancer.

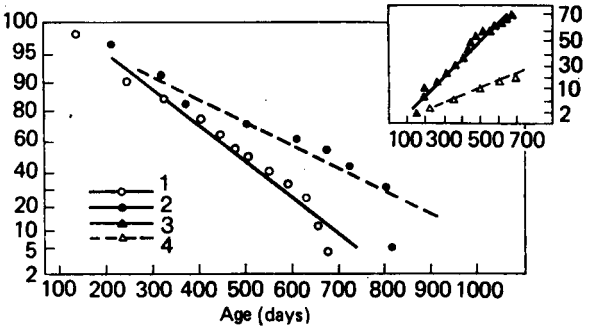

Fig. 9. The effect of phenphormine on longevity and breast cancer incidence: 1—control mice; 2—mice treated with phenphormine; 3—breast cancer incidence in control mice; 4—breast cancer incidence in mice treated with phenphormine.

A similar influence on the development of certain age-related diseases and on the lifespan of animals has been found in epithalamine, which is extracted from the pineal gland. The choice of these preparations is based on the fact that, according to this author's concept, the key mechanisms of aging and the diseases linked with it are, on the one hand, an elevation in the hypo-

thalamic threshold to the regulatory signals, and, on the other hand, those secondary hormonal-metabolic shifts that in the final end cause the intensive utilization of fat instead of glucose as fuel. These preparations act on the key mechanisms indicated above*.

In addition, preparations that are derivatives of protein hormones, i.e., "anahormones" ("ana" indicates negation) were obtained in the experiment. The author uses this term to designate derivatives of protein hormones in which hormonal activity has been eliminated by a chemical treatment but one of the three properties of a protein molecule has nevertheless been preserved. The latter are: 1) the ability to accumulate in the target-tissue, thereby hampering the activity of the corresponding natural hormone; 2) the ability to induce the production of antibodies, which neutralize the activity of the natural hor-

* Currently, the most interesting practical results involve the possibility of improving immunity by normalizing fat and carbohydrate metabolism in middle-aged people (from 40 to 60 years of age) who have an elevated content of triglycerides and cholesterol in the blood and a decreased utilization of glucose (which is observed in 60 to 70% of people of this age). The possibility of detecting latent mental depression by means of the dexamethasone test, and in some cases, of reducing its adverse effect on the organism has also arisen.

mone; and 3) the ability to suppress the production of the natural hormone by negative feedback.

These three classes of anahormones have been designated as anahormones-inhibitors, anahormones-antigens, and anahormones-competitors, respectively. In particular, the former preparations inhibited the development of cancer in the mice.

At the same time, there are good reasons to anticipate better results if the diet and means for normalizing the functioning of aging mechanisms are combined. Alongside the ways stated above for normalizing the regulatory (ontogenetic) mechanism of formation of the major diseases, it is undoubtedly necessary to apply methods that inhibit the metabolic element of aging and the diseases linked with it (i.e., improve the DNA-repair systems, decrease the probability of impairment caused by free radicals, etc.).

Thus, useful means of influencing the aging process are gradually being found in many specialized branches of medicine irrespective of their current demarcation. Nobody should be surprised by the fact that medicines are transferred from the sphere of pathology to the sphere of physiology—aging—because "normal diseases" are a continuation of development.

Also, one should not be surprised by the fact that many of the preparations used by

us have been known for a long time. Simply, until the model of development and aging that has been presented in these essays was developed, pharmacology had never been given the task of seeking for means that could lower the hypothalamic sensitivity threshold to regulatory signals. But in medicine it frequently happens that means are lacking until the goal is named and the desired effect is formulated, and then the necessary means are frequently found among existing preparations that have been used in medicine for quite different purposes.

Certainly, it is difficult to predict how effective the preparations used in an experiment on animals will be in the case of humans, and whether side-effects will be revealed that prevent their systematic application, although definite clinical results are currently available. Work is still to be done concerning this. However, we are speaking here not of specific medical problems but of the possibility of rendering a favourable influence on the course of age-related processes.

Today, the significance of this problem has increased owing to the progress of civilization, which, having extended the average lifespan, has simultaneously created conditions for activating the inherent mechanisms of aging and disease-formation. We must interfere in this contradictory

influence of civilization with no fear of the unnaturalness of such an experiment. After all for a century nature has been undertaking its experiment on extending the lifespan. During the years that have been won back from death many people suffer from serious diseases. Indeed, there is no more time to wait, it is the time to act.

Chapter 17

On the Path to Integral Medicine

To explain the identity of the metabolic patterns observed in pregnancy, stress, normal aging and major diseases is the problem that any theory of medicine is expected to provide an answer to.

In science it is not the facts themselves that are so important: it is their interconnection, which establishes the causal and consequential relations between them. In essence, this is the beginning of scientific *generalization and of the integration* of uncoordinated facts into a system, i.e., not simply the objects but the nature of the objects and their meaning in the general picture of nature are cognized.

It was comparatively recently that the process of integration in medicine began. In the nineteenth century the determination of individual diseases and their specific features was a prevalent trend. This was quite necessary because medicine could not develop without understanding the essence of each individual disease. Throughout the previous centuries, dozens of medical disciplines with the subsequent subdivision of each one had developed from the philosophy and medicine of the

ancients. The process of differentiation intensified in the twentieth century. Specialists appeared who knew a lot about rather limited branches of medicine but not about the subject as a whole. This resulted in the creation of specialized clinics. The whole was lost in the plurality of details.

But simultaneously, along with differentiation, arose the requirement for synthetic ideas. One of them was the concept about the leading role of disturbances in the nervous system in the development of many diseases. The classical works of I.P. Pavlov, V.M. Bechterew, L.A. Orbely, P.K. Anokhin, and their followers made it possible to determine the role of the nervous system in a large group of diseases that are related to disturbance of the nervous system, e.g., hypertension and ulcer.

At the same time, investigations undertaken by A.A. Bogomolts and his school introduced many new concepts explaining the pathological significance of another integral system of the organism: the reticulo-endothelial system, and then the immune system. Based on such fundamental studies, which outlined the role of integral functional systems in the development of diverse pathology, it became possible to search for a common system not based on morphological indications but on the developmental mechanism of diseases with different symptoms. For example, the hypotha-

lamus combines the properties of nervous tissue and an endocrine gland; therefore, to understand hypothalamic pathology, it is more important to determine how the functional state of the hypothalamus is associated with the onset of a disease than to classify it as a nervous or endocrine disease.

This functional association represents a very important step forward in the development of medical knowledge. Lang's concept of hypertensive disease as a certain hypothalamic pathology had a significant influence on the development of concepts about many other diseases, including oncological ones.

Another major generalization was made by H. Selye on the diseases of adaptation (see Chapter 2). Examining the organism's reaction to various infections and damages, Selye focussed on the common symptoms that are characteristic of many diseases rather than on their specific features. The common manifestations in diseases of various origin led to the idea of searching for common mechanisms of their origin. Thus, it gradually became clear that the mechanisms of protection (adaptation) against damaging factors can lead to the onset of diseases of adaptation. This group of diseases is characterized by various manifestations that are united by a common mechanism of functioning and disturbance of the organism's adaptational systems.

Today, however, even such a large functional division seems insufficient. In addition, it attributes a dominating role to external factors in the development of the major human diseases, which in many aspects is incorrect. More successful has been the attempt to view the organism as a system consisting of three supersystems that determine the basic functions of a living organism, i.e., the energy, adaptational, and reproductive homeostat, taking into consideration the fact that these three supersystems interact with one another. The following example illustrates this by describing a series of events within the framework of the integral model of interaction of the three homeostats.

Let's assume that a stress reaction emerges as a result of a word or phrase. This reaction, if it is sufficiently expressed, involves all the systems of the organism, from the brain to the genes in each cell of the body. For example, a word said with negative emotion is perceived via the auditory organ by the cerebral cortex. The information is then transmitted by signals to the subordinated departments: the limbic system and the hypothalamus. The activity of the hypothalamus increases and the organism's metabolism changes: in particular, the cholesterol concentration in the blood rises. Thus, the process, which was initiated by a word, consecutively involves the endo-

crine system and the tissues of the body, such as the liver where cholesterol is synthesized. The surplus cholesterol that circulates with the blood is supplied to the membranes of the cells, i.e., the internal environment, whose constancy as a condition of life was stated by C. Bernard, is disturbed. This thesis also applies to the tissues, which require the same degree of constancy as does the internal environment of the organism. But the surplus cholesterol that enters the cells (initially the plasma membrane), such as the lymphocytes, disturbs their functioning. In particular, it decreases their capacity for division by limiting the synthesis of deoxyribonucleic acid (DNA). In turn, this may induce diseases such as metabolic immunodepression. This is an example of true unity of "body and spirit", an example of the actual integrity (unity) of the organism, its physiology and pathology, normal and disease states, which is inevitably destroyed in the surprisingly fine specialization of modern medicine.*

In real conditions, the work of all the systems of the organism is coordinated

* In light of this example, the mechanism of metabolic immunodepression (in which an essential role is played by the accumulation of cholesterol in the plasma membrane of lymphocytes) as a variant of pathophysiological membrane shifts that form the picture of aging and the diseases linked with it must be considered.

and their activity preserves the constancy of the internal environment, i.e., homeostasis. The concept of homeostasis itself originated owing to the fundamental works of C. Bernard and W. Cannon (at the end of the ninteenth and beginning of the twentieth centuries). They clarified the conditions that are necessary for the existence of the organism, and explained the mechanisms for maintaining stability in it.

At the same time, owing to the fact that development of the organism requires a disturbance in the stability, mechanisms that ensure deviation of homeostasis also exist. But, since the side (undesirable) effects of this deviation accumulate very gradually after the end of the growth, they are most vivid in the aging organism. For this reason, a new integral association has appeared based on the study of the mechanism of aging, though it is not restricted only to the events occurring during this period. At different stages of constructing this integral model, various definitions of its tenets have been suggested. Let us discuss them briefly in order to show that, although much has been corrected in accordance with the new data and the general development of biology and medicine on the whole, in actual fact the trend of thinking has not changed.

This author first suggested that changes

in the activity of the hypothalamus play a certain role in the mechanism of aging, especially as far as age-related diseases are concerned, and these changes were determined to be due to an increase in the activity of the hypothalamic centres (V. Dilman, 1956, 1958). The proposition that there is an age-related elevation in hypothalamic activity preserved its significance for the changes occurring in the reproductive homeostat (Chapter 5). In 1968, this position was corrected based on the fact that the elevation of the hypothalamic sensitivity threshold was ascribed to the action of regulatory homeostatic signals. This more accurately characterizes the changes in the adaptational and energy homeostat (Chapters 4, 6-8).

Soon after, B. Stoll (1972) suggested that the decrease in the concentration of neuromediators directly induced the elevation in the hypothalamic threshold, and C. Finch (1973) explained that the rate of formation of one neuromediator—dopamine—slowed down during aging. In 1976 this scientist made an interesting attempt to explain this phenomenon by the impairing influence of peripheral hormones, in particular, hormones of the adrenal cortex, on the central structures of the brain, including the hypothalamus (cascade theory of aging). Subsequently, the association between the decrease in the concentration

of neuromediators in the hypothalamus, first and foremost dopamine, and the elevation in the hypothalamic threshold of the reproductive system was established in our laboratory by means of pharmacological analysis. In 1974, G. Cotzios and co-workers achieved an extension in the lifespan of rats by administering L-dopa, the precursor of dopamine. At the same time, L. Labori (1975) made an attempt to combine the regulatory theories of aging with cell theories, paying special attention to the role of intracellular managers of hormonal activity, viz., cyclic adenosine monophosphate (AMP) and cyclic guanosine monophosphate (GMP), and in particular, to how the synthesis of these mediators is dependent on the metabolism.

Later, G. Roth (1982) demonstrated that during aging the number of hormone receptors, e.g., receptors of corticosterone (or cortisol), decreases in different parts of the brain, in particular, in the hypothalamus. These changes cause disturbances in the regulatory mechanisms, in particular, a decrease in the sensitivity of cerebral structures to regulatory (hormonal) signals.

Thus, certain concepts about the factors that alter the hypothalamic feedback mechanisms during ontogenesis currently exist. On the whole, however, the primary reasons for this phenomenon are not yet clear; therefore, it is necessary to operate with

some fundamental propositions, which can be summarized as follows.

Nature functions through common laws whose dialectic essence is not always obvious. As applied to the problem discussed in this book, these are the laws of development. On the other hand, the existence of the organism itself depends on the maintenance of equilibrium and stability at the expense of both the inflow of energy and building substances and the activity of the systems in the organism that ensure the regulation of this inflow. This thesis has been reflected most fully in the law of C. Bernard, according to which the free life of the organism is possible only on maintaining the constancy of the composition of its internal environment.

At the same time, this fundamental law is incompatible with the developmental requirements of the organism because constancy prohibits development. Therefore, if the condition of life is stability, then, equally, the condition of development is the programmed disturbance of stability. Alongside the law of constancy in the organism's internal environment is the law of deviation of homeostasis, or, to be more precise, both these laws reflect the unity of opposites that ensures the development and existence of a developing living system.

In other words, the law of constancy of the homeostasis and the law of deviation

of homeostasis are two manifestations of one common law. After this author formulated the law of deviation of homeostasis between the years 1979 and 1981, the integral model of development, aging, and age-related diseases obtained its modern form, and the range of phenomena it described greatly expanded. Let us now discuss some direct consequences that follow from the new integration of facts. To do so, we must imagine a situation that is not very realistic.

A 56-year-old woman enters the clinic's reception room, which is divided into several booths. Each booth is occupied by a doctor, who is a specialist in only one, although wide-ranging, medical speciality. The patient has brought the results of laboratory tests. The doctors have to determine whether or not she is ill, and if she is, then with what. But although each of these specialists knows everything in his or her own particular field, he or she knows very little about other fields. In theory, this situation is not unrealistic if we take into account the fact that one good book on diabetes mellitus alone was written by 51 authoritative specialists. The division or differentiation of science can reach even such limits.

Thus, the patient enters the first booth where she finds an endocrinologist. According to her test results the doctor determines

that she is suffering from diabetes mellitus and assigns her to the endocrinological department for treatment (Table 9). But

Table 9. Cancer of the Uterus: an Integral Disease Case

Type of disturbance	Frequency of occurrence
1. Hypertension	Approximately 40%
2. Obesity (deviation of body mass from ideal, %)	21%-72%
3. Increase in triglyceride and cholesterol level in blood	64.1%
4. Age of menopause (climacteric)	51.9 years (49.5 years in controls)
5. Climacteric bleeding	27.7%-59% (14% in controls)
6. Dexamethasone test (hyperadaptosis, mental depression, cushingoid features)	18% decrease in blood cortisol level (45% in controls)
7. Metabolic immunodepression	In majority of patients
8. Auto-immune processes	25% (6.8% in controls)
9. Birth of a large fetus; 4 kg and more (acceleration of development)	50% (17.7% in controls)
10. Diabetes mellitus (subclinical, latent, and obvious)	63%-73% (20% in controls)
11. Decrease in blood growth hormone level after glucose load	6% (11% in age-adjusted controls, 50% in young adults)

since the patient had to be examined by all the specialists, at the conclusion she had received assignments to ten different specialized departments.

The general practitioner insisted on treating hypertension and also recommended metabolic therapy because of the patient's obesity, and treatment for heart problems because of the high level of triglycerides and cholesterol in the blood, which is a risk factor for atherosclerosis. After a lot of trouble the gynecologist discovered a late climacteric in the patient (at the age of 56, 6 years later than the average) and, at the same time, early switching on of the reproductive cycle. The patient was assigned to a gynecological clinic because of climacteric bleeding (which in the course of several years started and stopped spontaneously).

The psychiatrist quite reasonably suspected the presence of latent mental depression (Chapters 4 and 11) after observing the decrease in sensitivity to the action of dexamethasone. An immunologist also participated in this perfect medical examination, and immediately made two diagnoses: metabolic immunodepression, and, possibly, autoimmune affection of the thyroid gland.

The pediatrician was worried by the fact that thirteen years before the woman had given birth to a baby whose weight was in excess of 4 kg. Having studied accelerated

development, he had frequently observed this phenomenon, i.e., the combination of a late birth with a large fetus. He suggested that the patient and her daughter should consult a specialized pediatric department for a diet for the girl that would prevent obesity, which is one of the symptoms of accelerated development and which increases the probability of an earlier onset of certain diseases (Chapter 14). In contrast the gerontologist found indications of early aging in the patient because almost all of the test results exceeded the so-called age norm.

In the final end, the patient was hospitalized with a diagnosis of cancer of the uterus body, which was determined by the oncologist.

The oncological surgeon correctly decided that an operation was necessary. But the anaesthesiologist had to temporarily postpone the operation. Being a good specialist he knew that obese patients (who also have symptoms of diabetes mellitus) reacted worse to surgical intervention. In addition, the presence of hypertensive disease, the changes in the ECG (indicating atherosclerosis of the cardiac vessels), and, especially, the depressed mood of the patient (symptoms of mental depression) put the anaesthesiologist on guard. The postoperative period is more difficult in such patients: thrombosis of the blood vessels is more

probable and complications frequently appear during healing of the surgical wound. The level of prolactin also sharply rises in the blood of these patients during the operation and this may induce a progressive tumorous process. For these reasons a consultation was convened including all the specialists.

But, unfortunately, each specialist suggested his own method of treatment. In other words, each of the ten diseases found by this thorough examination was considered separately. Just a glance through this book will already have informed the reader that this approach is highly incorrect.

The previous chapters dealt with mechanisms that participate in the development of all these diseases and have many common features. This relationship is most clearly revealed by the signs that characterize common normal aging. Knowing this the oncologist turned to the endocrinological laboratory of the institute where they tried to find everything that related the ten major diseases with one another and with normal aging of the organism. Let's conditionally call the doctors of this laboratory doctor-integrators.

The head of the laboratory first of all focussed attention on the test that demonstrated an insufficient decrease in growth hormone (the main fat-mobilizing hormone)

in the patient's blood after the intake of glucose. There was an insufficient decrease in the blood cortisol level (the basic stress hormone) after the intake of dexamethasone (Table 9).

The reasons why these disturbances induce a shift in the organism towards intensification of the fat-based supply of energy and why this shift contributes to the development of the major human diseases was discussed in previous chapters. In addition, a disturbance in the adaptation system induces hyperadaptosis (which was confirmed by the results of loading with dexamethasone), as a result of which the organism must endure the burden of anti-stress protection, although it is not needed. And to protect oneself without need means to accelerate aging and to weaken the adaptation potential to real damaging factors when it is required.

According to the doctor-integrator, these disturbances were the initiating mechanism that led to the development of the totality of diseases in the patient. For this reason he transferred the data from the bottom of the list in the table to the beginning. Summing up the contents of this book, let's examine the mechanism of disease integration by the example of our patient (Table 10).

A change in the hypothalamic sensitivity threshold in the energy homeostat system,

Table 10. Hormonal and Metabolic Changes in Pregnancy, Aging, Stress, and "Normal Diseases"

Index / Phenomenon	Pregnancy	Aging	Stress	"Normal diseases"
Decrease in hypothalamic neuromediators	+	+	+	+
Cortisol	+	+	+	+
Growth hormone	+*	+**	+	+
Insulin	+	+	−	+
Glucose	+	+	+	+
Gonadotropins	+***	+	−	+
Thyroid hormones	+	−	−	−
Fatty acids	+	+	+	+
Cholesterol	+	+	+	+
Triglycerides	+	+	±	+
Thrombogenesis	+	+	+	+
Cellular immunity	−	−	−	−
Favourable effect of phenphormin on fat and carbohydrate metabolism	+	+	?	+

Note: + rise; − decrease; * placental growth hormone; ** decrease as obesity develops; *** chorionic gonadotropin.

which was manifested by the insufficient decrease in the growth hormone level in response to the glucose load, is precisely the disturbance that may cause decreased glucose utilization by the muscular tissue, i.e., prediabetes, and frequently type II diabetes mellitus. The glucose that is not

used by the muscular tissue transforms into fat. Thus, diabetes mellitus is followed by obesity, the second major human disease.

The absence of a decrease in the blood cortisol level after dexamethasone loading is also a result of hypothalamic disturbances. It has been stressed many times in this book that in the process of aging (alongside general obesity), unusual adiposity of mainly the face (moon-like face) and trunk arises, while accumulation of fat on the hands and feet is less expressed. This type of obesity is characteristic of a rather rare disease—Itsenko-Cushing's disease. But in a less conspicuous form this complex is characteristic of normal aging. Thus, another (fourth) "normal disease"—hyperadaptosis—develops (Chapter 4).

But, let us recall that the psychiatrist also noticed the unusual results from the dexamethasone loading. These led him to conclude that a fifth disease was present: latent mental depression. The fact is that the decrease in hypothalamic sensitivity to the inhibiting effect of dexamethasone is conditioned by a decrease in the concentration of neuromediators (dopamine and serotonin) in certain structures of the brain. This causes mental depression.

In addition, a decrease in the concentration of neuromediators increases the appetite and, correspondingly, induces obesity. This mechanism of the development of obesity

is taken into consideration by pharmacologists, who are working out ways of suppressing the appetite on the basis of substances that elevate the level of neuromediators in the hypothalamus.

Finally, the mechanism of the age-related switching-off of the reproductive function in the female organism is also linked with the decrease in the concentration of hypothalamic neuromediators. Thus, the climacteric—the sixth "normal disease"—develops in the integral mechanism (Chapter 5). For this reason, the gynecologist also had something to think about. The climacteric had already started in the patient by the time of the consultation. But since the climacteric mechanism is associated with an age-related elevation in the hypothalamic threshold in the reproductive homeostat, and patients with cancer of the uterus body demonstrate intensified aging, it is natural that in this disease the hypothalamic shifts in the reproductive homeostat are more expressed than usual. Indeed, it turned out that the patient's menstrual cycle had started at the age of eleven, which is an indication of accelerated development conditioned by early hypothalamic shifts (Chapter 14). There is also no contradiction between this indication of accelerated development and the fact that the reproductive cycle ceased functioning later than usual in the patient. If the hypothalamic

threshold to inhibition is elevated, then the hypothalamo-hypophyseal system, which is not held back by a reliable "brake", intensifies its activity. Indications of increased stimulation of the sexual glands, which is manifested in particular by climacteric bleeding, are found in the case of cancer of the uterus body.

However, despite the fact that functioning of the reproductive system in the patient was intensified, she did not conceive for a long time after marriage. This can apparently be explained by disturbances in ovulation because the more clearly the hypothalamic shifts are expressed, the worse this mechanism functions (Chapter 5). Thus, doctors have established that sterility (temporary or permanent) occurs during the reproductive years in 40% of women ill with cancer of the uterus body.

A decrease in the concentration of hypothalamic neuromediators occurs regularly during aging and, therefore, aging combines so easily with obesity, prediabetes (type II diabetes mellitus), the climacteric, hyperadaptosis, mental depression (in its obliterated form), and hypertensive disease (or, more precisely, a gradual rise in arterial pressure). The combination of all six of these diseases can be truly observed in 60 to 70% of patients with cancer of the uterus body; this indicates that they show signs of accelerated, intensified aging.

Thus, the factors that determine such a complex picture of disease as in the case of our patient integrate and gradually become apparent. All the listed above deviations are interrelated and united by one common element: the hypothalamic changes that are conditioned to a significant extent by the increasing deficit in hypothalamic neuromediators during aging.

But on the point of this "hypothalamic pivot" there is a metabolic group of diseases that is directly or indirectly strung. No special explanations are required if we recall the role of the hypothalamus in increasing the appetite and, correspondingly, inducing obesity (Chapters 6 and 7). The shift to intensified utilization of fat as fuel (which is characteristic of obesity) is increased by changes in the adaptational system, wherein the disturbances are responsible for the onset of hyperadaptosis. Meanwhile, obesity as well as hyperadaptosis contribute to the development of diabetes in obese people. This influence is easily understood if we recall that carbohydrates burn poorly in the flames of fat (Chapter 8).

The initial stage of this type of diabetes (as well as prediabetes associated with normal aging) is not characterized by a decrease in the blood insulin concentration; on the contrary, it is distinguished by an increase. The surplus of insulin in the blood together with the surplus of glucose sup-

ports the state of obesity, creating a vicious circle from which the organism is unable to escape without treatment.

As a result, patients often demonstrate an elevated concentration of fatty acids, triglycerides and cholesterol in the blood: these are the same changes that are characteristic of patients with atherosclerosis. This is the reason why the cardiologist established that disturbances in the cardiac activity were developing in our patient, while the anaesthesiologist apprehended the onset of thrombosis of the vessels in the postoperative period. Indeed, it is known that an elevation in the blood cholesterol level causes an increase of cholesterol in the thrombocytes. This sharply increases their capacity to aggregate with one another as occurs during stress when the organism shifts to the fat-based energy supply. When the thrombocytes aggregate, they release hormonal growth factors, and, if there is an excess of these factors, the development of atherosclerosis is stimulated (Chapter 9). Thus, the seventh disease of the ten major diseases arises: atherosclerosis.

Finally, all these changes in the concentration of glucose, insulin, fatty acids, and cholesterol suppress the cellular immunity (metabolic immunodepression). Thus, the immunologist was quite correct to insist on assigning the patient to a hospital because of the eighth disease (Chapter 9).

As is known, humoral immunity is stimulated (or distorted) with a decrease in cellular immunity. This causes the accumulation of antibodies against one's own cells as if the latter had become "foreign". Thus, with age there is an increased probability of the onset of the ninth major disease, which manifests itself in many ways in the so-called auto-immune diseases that either occur without any symptoms, or affect the tendons and joints, or, as in the case of our patient, reveal themselves by the increase in antibodies acting against the thyroid gland.

In addition, our patient suffers from the tenth disease: cancer of the uterus body. This is no surprise. The metabolic disturbances described above induce a state of cancrophilia, which increases the probability of the onset and progressive development of cancer (Chapter 10).

It is also quite probable that these metabolic shifts (first of all, the increase in the blood cholesterol level) prevent the repair of DNA, i.e., the elimination of mutations and other impairments of the genetic system, which activate cellular oncogenes (Chapter 10).

Thus, the same mechanisms are responsible for all of the ten major diseases of the middle-aged and elderly. These diseases are so closely interrelated that it is natural to ask the following question: are there

really ten individual major diseases, or is there one integral disease with ten major symptoms?

It is precisely the latter circumstance that created such an unusual situation when different specialists examined our patient. In reality, they met with manifestations of the mechanism of disease development that is uncommon in traditional medicine and that this author has called the ontogenetic model (Chapter 12). In light of the concept of the ontogenetic model of development of the major human diseases they should all, with a certain degree of expressiveness, arise with increasing age, creating the multiplicity of age-related diseases, because the mechanism of development of the organism is at the base of each one, and each major disease is a by-product of the realization of this mechanism.

The integration of the major human diseases is not something that researchers have thought up: it lies at the very essence of the phenomena. The researcher can only study the mechanism of integration, or, if captivated by individual profound problems, may not observe their interrelationship. But it is now clear that the integral approach allows one to search for an explanation of the interrelationship between all these diseases, and that as a result of this approach it is possible to indicate three new diseases, i.e., metabolic immunodepres-

sion, cancrophilia, and hyperadaptosis, which earlier had been masked from medical analysis by the elusive borders of the transitions from one disease to another. The *first* consequence of the integral model of medicine is the description of the interrelationship of the mechanisms of the major diseases.

Certainly, for practical purposes it is currently necessary and useful to isolate ten individual diseases from one integral disease. But, to understand the essence of the phenomenon, one should not forget that this demarcation is conditional. The essence is demonstrated most clearly by the example of the most universal disease—aging. To a certain extent aging is always characterized by nine major diseases. In addition, aging increases the risk of cancer. In a certain sense it is possible to agree with the statement that four out of every five people simply do not live to the age of their "own cancer" because other major diseases claim their lives. Thus, aging can be called the eleventh major disease: this is the *second* consequence of the integral model. But in the practical sense this formulation is unnecessary, because if aging runs normally, it does not cause any specific diseases and only exposes the major ones.

In turn, the complex of phenomena that are combined in the aging pattern is defined

not only by the accumulation of impairments caused by internal and external factors, but also by the specific features of the developmental mechanism of the organism. In other words, not only the major diseases, but also aging, is the by-product of the developmental mechanism, or, to be more precise, is the result of transformation of the developmental mechanism into the mechanism of aging and age-related diseases (*third* consequence).

At the same time, if the onset of the major diseases should be related because of unfavourable ecological and genetic factors to the class of random phenomena, then the ontogenetic mechanisms inevitably (because of a disturbance in homeostasis which is characteristic of these mechanisms) form the major diseases. Thus, in the absence of random causes of diseases and death, the onset of the major diseases and the natural causes of death are the result of regulatory disturbances. A very important conclusion is comprised in this *fourth* consequence: the possibility of counteracting the factors that currently are the cause of death in every 75 out of 100 people who are middle-aged or older.

It would seem that objections could be raised to this concept because not only internal, but also many external factors, are the direct cause of the onset of the major human diseases, and it is possible

to frequently observe the dominating influence of these external factors. But, as was stated many times in this book, the external factors that cause the major diseases, in reality, accelerate the internal mechanisms of their onset. For example, the protection (adaptation) mechanism against stressful and impairing factors of the external environment can be realized if certain hormonal and metabolic shifts are ensured.

In turn, these shifts can be maintained during the time necessary to realize the mechanism of protection only if the same changes occur in hypothalamic regulation that are also characteristic of the aging mechanism. Therefore, accelerated aging and age-related diseases are the price paid for protection. On the other hand, the factors that exert a similar effect on the state of the hypothalamus, e.g., continuous illumination, accelerate the aging process, and, in contrast, any factors that increase the hypothalamic sensitivity to the regulatory signals retard aging. The above discussion explains the *fifth* consequence of the integral model and makes it possible to combine the mechanisms of interaction of the internal and external factors of aging and age-related diseases into a single complex.

When extending the list of consequences of the integral model, it should be noted that all the factors that contribute to the

development of the major human diseases also accelerate the development of the organism (Chapter 14). And what is more, if accelerated development takes place in a female organism and is not counteracted, then aging is accelerated later on and the earlier development of age-related diseases is observed. In turn, there is an increased probability that this woman will give birth to a child with excess body mass, which may cause accelerated development in the next generation, and so on. In the final end, this leads to an increased number of people with accelerated development and with untimely development of age-related pathology in the population (Chapter 8). This is the *sixth* consequence determining the interrelationship in the integral model between acceleration of age-related pathology and accelerated development of the organism.

Here we confront the following problem, which is important from the practical point of view. It is quite obvious that a large fetus is a risk factor for the development of cancer of the uterus body. Other risk factors may include obesity, hypertension, and diabetes mellitus: in essence, all the other indications characteristic of "normal diseases", especially if they do not arise isolated but in combination with one another. Based on these considerations, as far back as 1973 this author substantiated the con-

cept of metabolic epidemiology of cancer. In particular, it is possible to gain a general idea about the anticipated incidence of cancer in various regions by studying the distribution of metabolic disturbances in those regions of the country. As a result, it is possible to elaborate measures to improve the metabolism of carbohydrates, cholesterol, and fat.

At the same time, in elaborating this *seventh* consequence of the integral model, attention should be focussed on the fact that the same disturbances are also an object of interest for the metabolic epidemiology of atherosclerosis and diabetes mellitus. The incidence of these three diseases—atherosclerosis, insulin-independent diabetes mellitus, and cancer—increases gradually with an increase in the influence of various harmful factors on the human organism (Chapter 11). Though the cardiologists, endocrinologists, and oncologists still individually seek risk factors for these three diseases, an attempt can be made to determine their common risk factors on the basis of the integral model.

This would be useful in many respects. For example, cardiologists who study the metabolic epidemiology of atherosclerosis have progressed in comprehending the processes more than other researchers. In particular, they have paid attention to the fact that an elevated level of α-cholesterol

(or, more precisely, the level of high-density lipoproteins) in combination with a decrease in β-lipoproteins, protects against the accelerated development of atherosclerosis, which contributes to longevity. But, it is advisable to determine these indices in oncology as well. This becomes increasingly obvious as epidemiological data accumulate on the role of surplus nutrition and especially surplus animal fat and cholesterol in the development of many types of cancer.

At the same time, according to a series of epidemiological studies, a low concentration of cholesterol in the blood (about 160 mg%, or 4.14 mmol/l) combines with an increased incidence of cancer, especially of the large intestine in males. On the basis of these observations one can conclude that there is some danger in decreasing the cholesterol concentration by means of treatment. However, it is not taken into consideration that an initially low concentration of cholesterol after the age of 50 is in itself an abnormal phenomenon because there should be an age-related elevation in the blood cholesterol level at this age. If there is no elevation, it may indicate the presence of other (usually genetic) disturbances, which promote an increase in the incidence of cancer (e.g., because of defects in the immune system, or increased excretion of cholesterol by the intestine).

Similarly, an exceptionally high concentration of cholesterol in the blood (more than 350 mg%, or 9.05 mmol/l) is commonly an indication of so-called familial hyperlipidaemia, a genetic disease characterized by a lack of lipoprotein receptors that accomplish the transport of cholesterol into the cell (Chapter 9). The incidence of cancer can be reduced in these cases, apparently because of the absence of metabolic immunodepression as a result of the insufficient transport of cholesterol into the lymphocytes. In other words, according to these criteria, one can divide the population into three subpopulations, and the normal subpopulation (making up more than 85% of the population) is characterized by a dependence between the age-related elevation in blood cholesterol levels and the onset of metabolic immunodepression, and, consequently, an increase in the probability of cancer development. Thus, for this largest subpopulation it is necessary first of all to attain an optimal concentration of cholesterol in the blood with the help of various methods (Chapter 16). In this way, the common risk factors and principles of prophylaxis of the major human diseases constitute the *eighth* consequence of the integral model.

Examination according to the system of the "Certificate of Health" is based on this principle because only the ontogenetic

model introduces the "counting-off point" in the form of an ideal (or optimal) norm, and a deviation from the latter leads to the development of the major (noninfectious) human diseases. This defines the *ninth* consequence of the model under consideration. Let's return again to our patient. All the specialists have assembled together at the consultation, including the doctor-integrator. Currently, the hydroxyprogesterone caproate-hormonal preparation is usually prescribed for treating cancer of uterus body: it retards the division of cells in the reproductive system and, at the same time, transfers them to the path of normal differentiation. However, a more complex method of treatment has been chosen because the patient had not one, but a combination of ten diseases.

At first, phenformin (or metformin) was prescribed: it is an antidiabetic preparation that improves the activity of the hypothalamus, reduces the production of gonadotropins, improves fat and carbohydrate metabolism and, thereby, immunological protection, normalizes coagulability of the blood, and reduces the activity of the adrenal cortex, which is high in patients with cancer of the uterus. Then hydroxyprogesterone caproate was prescribed in conformity with the commonly adopted scheme of treatment.

The *tenth* consequence of the integral

approach is the use of preparations that are commonly applied in other spheres of medicine. The integral approach allows the use of common means for treating various major diseases. The division into medical specialities does not exist in the organism. There are common regularities in the organism and they can be manifested in various diseases. Thus, dietary restriction and a proper diet are used when treating not only obesity, but also atherosclerosis, diabetes mellitus, metabolic immunodepression, and cancer.

Let's now discuss the *eleventh* consequence of the integral model. This consequence is so important that it is first necessary to consider some classical problems that emerged in gerontology almost 160 years ago. In 1825, B. Gompertz, a British researcher, studied the dependence between age and mortality. He found that the probability of death with age rises exponentially (i.e., in geometric progression). Contemporary statistics confirm this dependence in the interval between the ages of 30 and 80, wherein mortality doubles approximately every 8 years. Figure 7 illustrates a typical situation, where the most diverse reasons for death are subordinated to a similar increase in the death rate, first and foremost, death as a result of the major (noninfectious) diseases. Naturally, explanations for such a regular

and vivid fact have been sought for many years, including the modern period of gerontology. Leaving aside the details of this complex problem, which is commonly studied by mathematical methods, we shall note only that it is usually accepted that Gompertz's curve corresponds to the situation when random variations in the internal and external environment of the organism are the direct cause of death. This assumption is made to coordinate the linear (gradual) age-related decrease in the functions of the organism during aging with the exponential (geometric) increase in age-related mortality. It is believed that death sets in when the homeostatic systems in the organism are unable to restore equilibrium, which has been disturbed by fluctuations in the internal and external factors (B. Strehler, *Time, Cells and Aging*, New York, Academic Press, 1977).

At the same time, it follows from the ontogenetic model that the deviation of homeostasis regularly increases and, therefore, random events (or fluctuations) can define only the time, and not the cause, of death. In addition, the exponential type of mortality curve (which is commonly considered as an argument in favour of the primary role of random factors in the causes of death) can be defined in accordance with the ontogenetic model by two circumstances.

On the one hand, in any normal population each physiological index, such as the concentration of cholesterol (or low-density lipoproteins) in the blood, is subordinated to normal (Gaussian) distribution. For example, one study demonstrated that the blood cholesterol levels in schoolchildren between the ages of 8 and 16 range from 120 mg% to 280 mg%. When according to the law of deviation of homeostasis the gradual increase in this index occurs, individuals with an initially high cholesterol level will more quickly reach the degree of disturbance in homeostasis at which pathologic changes that are incompatible with life appear. Indeed, based on observations carried out for many years it has recently been established that the blood cholesterol level in childhood largely predetermines the value of this index upon reaching middle age. Therefore, the ever accelerating shift, at which the number of individuals increases who reach the limit disturbance in homeostasis, can determine the nonlinear character of mortality increasing with age. Though the given example considers the age-related "drift of cholesterol", it is applicable for the other indices of age-related deviation of homeostasis, a deviation that induces the major human diseases.

On the other hand, the increasing deviation of homeostasis and the development

of hyperadaptosis in a greater number of individuals (see Chapter 4) will lead to inadequate (excessive) deviation of homeostasis in the presence of a decreasing influence on the part of the external environment. In other words, the dependence of mortality on external effects is defined not only by the exponential distribution of the fluctuations in the external disturbing (impairing) factors from larger to smaller ones in force, but also by the change in the subject's reaction from a less intensive to a more intensive one, i.e., from a less impairing reaction to an inadequate protective (adaptational) reaction that is incompatible with life.

These rather complicated concepts are presented for the sole purpose of explaining one of the most harmful prejudices that has appeared in medicine as a result of the incorrect interpretation of Gompertz's curve. Let us return again to Fig. 7. Since the probability of death doubles after the age of 30 every 8 years irrespective of the disease that caused it, the conclusion is drawn that aging itself is the real cause of death. This leads to the belief that if it were possible to eliminate any one of the major diseases, this would negligibly reflect on the average lifespan. For example, if mortality as a result of tumours were eliminated, then the lifespan would increase by two or three years. Indeed, if the mor-

tality due to tumours is deducted from the total mortality, then the curve shifts slightly to the right, which corresponds to a two- or three-year increase in the average lifespan.

Calculations indicate that the elimination of mortality due to atherosclerosis and its complications extends the lifespan by ten to twelve years, insofar as in this case mortality increases as a result of cancer, infections (because of metabolic immunodepression), stress (because of hyperadaptosis), traumas (because of carelessness, or suicides associated with mental depression), or diabetes mellitus, in other words, because of any other disease, as aging itself is the sum of diseases of homeostasis, that reduce the resistance and enhance the vulnerability of the organism.

But it follows from the ontogenetic model of disease development that an increase in the lifespan can be attained by retarding the rate of the aging process itself because it is the ontogenetic model of the development of the major human diseases and only this model that links for the first time the origin of the major human diseases with the organism's developmental mechanism. This conclusion, according to which it is necessary to slow down the rate of aging in order to retard the rate of development of the major diseases, is the eleventh consequence of the

integral model. In addition, the concept of the ontogenetic model of the origin of diseases explains why the successful treatment of any one major disease, if it is achieved, cannot greatly influence the index of age-related mortality and why it is necessary to search for means that could influence all or the majority of major diseases as a whole group. This is the *twelfth* consequence of the integral model.

Finally, let us address the *thirteenth* consequence. As is known, the difference between the average lifespan in industrially developed countries, which is about 70 to 75 years, and the maximal lifespan of humans, which is from 110 to 120 years, is quite large. This difference is conditioned by the fact that the average lifespan mainly depends on the genetic and ecological reasons for death, while the maximal lifespan depends on ontogenetic and accumulational ones. The individuals in whom genetic and ecological factors lie at the basis of the major diseases do not usually reach the age that is average for the entire population, and the purely accumulational mechanisms of development of the major diseases are insufficiently pronounced by the age of 70 or 75. Hence, if we learn to counteract the ontogenetic mechanisms, the modern average lifespan can be made to approach the modern species lifespan. From this point of view it should be under-

standable why any modern programs for extending life are utopic if the regularities expounded in this consequence are not taken into consideration.

Thus, the ontogenetic model of development, aging, and diseases is an attempt to describe in one mechanism such externally different physiological and pathological processes as the metabolic background of pregnancy, the growth and development of the organism after birth, accelerated development, the mechanism of switching the reproductive function on and off, common regularities in the origin of specific age-related pathology ("normal diseases") such as the climacteric, age-related obesity, hyperadaptosis, prediabetes, atherosclerosis, hypertensive disease, metabolic immunodepression, auto-immune diseases, mental depression, cancrophilia (conditions contributing to the development of cancer), and causes of natural death.

This mechanism lies at the basis of untimely development of specific age-related pathology and accelerated aging under the influence of such factors of the external environment as acute and chronic stress, overeating, excessive illumination, chemical carcinogens, and so on. Taking into consideration everything that has been stated above, this author believes that any other theory on the origin of the major human diseases should also address the

question on the connections between all these phenomena: it should explain the reasons for the similarity between the metabolism during pregnancy, aging, stress, and age-related diseases (Table 10). Apparently, this is possible only within the given ontogenetic model.

However, this does not mean that many other facts and explanations are incorrect, or have lost their significance. And what is more, having described the ontogenetic model, it becomes possible to demarcate the data pertaining to the ontogenetic model and other "models" of diseases, i.e., ecological, genetic, and accumulational (involutionary) (see Chapter 12). And this in turn, allows one to approach the development of prophylaxis and treatment for the major human diseases in different ways, taking into consideration the various mechanisms of their formation.

Thus, if the prophylaxis of any major disease that arises under the influence of ecologically unfavourable factors demands measures for the elimination of these damaging factors, or if a genetic predisposition makes it necessary to correct the available defect, then a disease that develops in accordance with ontogenetic regularities, especially if it arises prematurely, demands means directed at retarding the rate of aging (see Chapter 16). It follows from the aforementioned that we are deal-

ing not with various models of the onset of diseases, but with various models of medicine because they include not only the mechanisms of disease development, but also substantiation of their prophylaxis and treatment. Hence, according to the *fourteenth* consequence, integration is impossible in medicine outside the ontogenetic model.

As far as other consequences of the integral model are concerned, it should be noted first of all that natural selection influences the organism through ontogenetic mechanisms. Thus, in conformity with this *fifteenth* consequence, a decrease in mortality due to external causes results in an increase in the maximal species lifespan, and vice versa (Chapter 11). In the final result, the length of the maximal lifespan is not invariable and, therefore, it can be increased by retarding the rate of realization of the ontogenetic and accumulational mechanisms.

In addition, the integral model makes it possible to combine stochastic and deterministic phenomena that form the mechanisms of development, aging, diseases, and natural death. For example, according to this *sixteenth* consequence, damage caused by by-products of metabolism, in particular, free radicals, participates in the formation of hypothalamic mechanisms of ontogenesis.

Finally, and this is the *seventeenth* consequence, the integral model exposes and illustrates the dialectic interrelationships in the organism, as is shown in this book first by the example of the interaction between the constancy of homeostasis and the law of deviation of homeostasis. The consequence of this interaction is the absence of a division between development and aging, between aging and diseases, and between the norm and the major diseases. From this point of view, it is easy to understand why the widespread method of eliciting the causes of diseases, or their risk factors, which is based on "case-control" comparison and is quite adequate when studying the ecological or genetic model of the onset of disease, is inapplicable for the ontogenetic model. Thus, the same state of immunity is observed in the "case" group and the "control" group when examining the reasons for the age-related increase in the frequency of cancer. As a result, the conclusion is drawn that the decrease in immunity is not a condition contributing to the onset of cancer. But this conclusion is erroneous because an age-related decrease in immunity in relation to the ideal norm has already occurred in both groups (Chapters 9 and 13), which may predetermine the age-related increase in the frequency of cancer in the population, but the onset of the disease

in an individual depends on another category of phenomena, i.e., on accidental damage to the genetic apparatus of the cells.

As a result, natural death limits the lifespan of each individual, although this limit is not imposed by natural laws. In other words, nature, having in this case no goal, nevertheless reaches it in the best way.

Thus, unity reveals itself through the separate parts of medical knowledge and destroys the borders between individual specialities. And thought begins to return to the lost integrity that existed in ancient medicine. But this synthesis is unthinkable without merging the individual disciplines that transform the human body into an artificial mosaic.

The necessity for integration in biology and in science as a whole is widely felt. The limited nature of a scientific approach based on the principle of specialization is obvious, but currently it is possible to approach the creation of a model of integral medicine only by combining the ontogenetic model of medicine with its other models.

Hence, the integral model does not demand repeal of that which is known, and does not dispute anything that is a trustworthy fact, but it determines the borders of applicability of the known facts and conclusions, often making it necessary to reinterpret them.

Epilogue

From dreams... to discovery.

H. Selye

And from discovery... to new dreams...

Let us imagine that it is the 21st century. If anyone wished to compare the achievements of biomedicine in the 1980s with those of the new period (for convenience let's call them the first and second periods), one would see numerous ties between them. Nevertheless, the changes would be striking.

Already during the first period it was hypothesized that if the duration of development and maturation of the organism were extended, it would be possible to greatly increase the maximal lifespan (Chapter 11). For example, R. Cutler stated that if the maturation period were 50 years, the average lifespan would increase to 250 years. For this reason, special methods were applied to prolong the period of sexual maturation. In addition, embrional cells were examined during the early stage of pregnancy to detect defective genes. A scientific school that investigated the prevention of genetic defects arose. Followers

of this school fertilized an ovum outside the organism and then, after genetic examination of the embryo, transplanted it into the organism of the future mother who had been treated with the required hormones. (Finally, a radical scientific school originated from the concept that the entire period of embryonal development should take place outside the organism, but this trend had few followers because of objections based on ethical grounds.) The state of metabolism in the mother's organism was controlled very strictly during pregnancy to fully prevent accelerated development of the fetus.

Childhood and youth in the second period have changed radically as compared to our time. Under the new conditions foreign languages are intensively studied according to the so-called maternal mechanism and anyone can easily master them. In addition, as is known, the aptitude for physics, mathematics, or chess is usually revealed at an early age and prolongation of the maturation period (neoteny) contributes to the rapid development of the exact sciences and, correspondingly, their application. Retardation of the rate of maturation slows down the rate of development of the major human diseases in accordance with the ontogenetic model. These diseases start to develop mainly between the ages of 180 and 200.

But the described method of extending the lifespan is neither the only, nor even the basic, one. It follows from the ontogenetic model that the development of diseases can be sharply retarded if homeostasis is stabilized at the level that is reached when the organism's development has ceased. At the same time, this stabilization should decrease the vulnerability of the organism to any damaging (and pathogenic) factors. In any case, according to the calculations of R. Cutler, if it were possible to stabilize mortality at the level of the 30-year-old adult in developed countries in the first period, the maximal lifespan of humans would increase to 1246 years, and 50% of the population would live more than 374 years.

It is natural, therefore, that studies on the stabilization of homeostasis as well as the elimination of random damages at the cellular level proceeded at a fast pace. Works of this kind have already appeared in the first period. One of the cardinal disturbances in homeostasis, which is followed by the succession of major human diseases—obesity, type II diabetes mellitus, atherosclerosis, metabolic immunodepression, and cancrophilia—occurs because of a decrease in the sensitivity of the tissue to insulin. In light of the genetic model this disturbance in people suffering from type II diabetes mellitus was assessed as a ge-

netic defect that is not detected immediately, but usually between the ages of 40 and 50. Therefore, the investigation, demonstrating that only freshly obtained cells (fibroblasts) from patients suffering from the given form of diabetes mellitus (i.e., a disease similar, in essence, to that occurring in the case of normal aging) are less sensitive to insulin, was highly significant for the development of concepts related to the ontogenetic model of disease development. When these cells are kept for several days outside the organism in normal medium, their sensitivity to insulin normalizes. This means that it is not the genetic effect that is to blame for the disturbance, but the change in the internal environment of the organism where the cells lived. When this environment normalizes, there may be no disturbances at the cellular level that induce the development of diabetes mellitus and related diseases.

Doctors have gradually learned to maintain homeostasis near the level characteristic of the end of the growth period of the organism. Certainly, it took some effort to accomplish this goal, because methods to preserve the internal environment of the organism, and adequate regulation, particularly, at the hypothalamic level, had to be found. As was mentioned in this book, the recovery of the cyclic functioning of the reproductive system in animals

(Chapter 5) and of the adaptational system in humans (Chapter 4) was proved possible already in the first period by pharmacological means; therefore, it is no surprise that studies in this direction have been successfully pursued.

Thus, it has gradually become possible to control the ontogenetic mechanism of disease development. However, certain practical difficulties have remained because permanent medicinal counteraction to the ontogenetic mechanism of disease onset must be maintained. In principle, means and methods for the steady stabilization of the regulatory mechanisms at the optimal level can be found (see below). It should be noted that prejudices against synthetic products and medicinal means, in particular, gradually disappeared. Such hormones as insulin and growth hormone were already biosynthesized in the first period.

At first the amino acid composition of human insulin was determined, and the gene coding for insulin was artificially synthesized. By clever manipulations this gene was introduced into common bacterium, *Escherichia coli*, myriads of which soon started to produce the insulin that was required for patients. Direct methods for isolating the necessary genes from the set of human genes were soon developed. In-

sulin no longer had to be extracted from the pancreas of animals.

Subsequently, it became possible to obtain all required proteins in this way: an unlimited quantity of the component parts of animal food could be produced outside the organism of "our smaller brothers". This achievement heralded a new era that could be called the era of neovegetarianism because one can eat products of animal origin since they are produced without killing animals. Gradually, everybody started to consider synthetic food as natural, and the former food—natural products—as unnatural and below human dignity. Therefore, prescriptions for various biosynthetic drugs were easily accepted, and those who wished to counteract the ontogenetic mechanisms of development of the major diseases started regularly taking the necessary preparations.

But studies were simultaneously carried out in the field of genetic engineering of the hypothalamus in order to attain the genetic (not medicinal) stabilization of the hypothalamus (and associated nerve centres) at the optimal level (see below).

It may seem strange, but the situation remained much worse in the sphere relating to the involutionary, and especially the ecological model of the onset of the major diseases. The environment still remained polluted to a significant degree

because its decrease depended on a series of social factors, such as a decrease in the consumption of the "advantages of civilization" (transport, microwave radiation, etc.). This all served as a source of external damaging factors that combined with the internal (metabolic) damaging factors. Certainly, in this period a new method has been discovered for transforming normal somatic (body) cells with a limited lifespan into immortal ones, but this method does not concern tumour cells.

This direction in research was also started in the first period. In 1983 it was announced that the DNA structure of the herpes simplex type II virus contains a fragment that may introduce properties of immortality into somatic cells without transforming the latter into tumour cells.

As is known, already at the end of the nineteenth century it was hypothesized that germ cells, in essence, were immortal because they were passed from one generation to another over many millennia. Immortality is also characteristic of tumour cells. Although it is commonly accepted that biochemical processes inevitably damage cells, thereby conditioning their metabolic aging (Chapter 11), the energy reactions in cancer cells proceed still more intensively, which does not prevent their practically infinite existence in time (po-

tential immortality*). It follows from the aforementioned that it is more likely the regulatory, and not the metabolic, mechanism of aging that predetermines at the level of the individual somatic cell the finiteness of its existence. Thus, nature "knows" the principle of avoiding irreversible consequences of cellular (metabolic) aging but this principle is realized only in the sex cells and malignant cells.

Taking all these prerequisites into consideration, experimental animals were developed in whom each somatic cell was immortal (this was achieved by introducing corresponding fragments of viral DNA, or certain oncogenes (see Chapter 10) during the early stages of embryonal development). But the totality of all cells still made up another "mortal body" for which regulatory disturbances were the cause of natural death. Nevertheless, this achievement represented a step forward in realizing the potential immortality of cells in a human. Meanwhile, intermediate mea-

* It is possible to imagine that the repeating division of cancer cells ensures a high degree of "defect dilution", or that randomly undamaged cells are selected in the process of division and it is these cells that are preserved. However, both phenomena are unable to fully ensure the absence of an accumulation of damage if it is born in mind that cancer cells are "infinite" when transplanted from one animal to another, or in cell culture.

sures were applied in the second period. The following are two examples of such measures.

As is known, during the organism's development the nerve cells of the brain lose the capacity for division. The "logic of nature" is quite clear. Each nerve cell is connected by its fibres with a plurality of other nerve cells, which creates the "miraculous network" of intercellular relations, which lies at the base of cerebral activity. If the nerve cells did not lose the capacity for division, then at each division the necessary connections would be broken. For this reason, the neurons of a mature brain lose the capacity for division. Defects that are a result of damage accumulate in time mainly in nondividing cells. This is clearly illustrated by the accumulation of senile pigment, i.e., lipofuscin, in the nerve cells of the brain (Chapter 12).

Certainly, when it was possible to ensure that each somatic cell, including the nerve cells, became "potentially immortal", the retardation of metabolic aging of the neurons was induced. At the same time, the mechanism that inhibited their division was unravelled. The blocking of cholesterol synthesis turned out to be an important element in this mechanism.

It has been known for a long time that mature nerve cells neither divide, nor synthesize cholesterol (nor, correspondingly,

transform into cancer cells). The capacity for division was renewed when it was found how to unblock the synthesis of cholesterol. This novelty turned out to be applicable to certain hypothalamic cells whose activity was not associated with the transmission of a neural signal and with the production of hypothalamic hormones.

As is known, hypothalamic cells are impaired, first of all, by the hormones of the peripheral endocrine glands that function in the feedback mechanism (see Chapter 11). For example, impairment of the cells of the hypothalamic arcuate nucleus by sex hormones plays an essential role in the changes that ensure the age-related switching-on and off of the reproductive function. Now, the damages are eliminated in these cells during the process of division*. As a result, the mechanism of hypothalamic regulation was recovered.

The second complex of measures for overcoming local manifestations of aging was associated with the solution of a series of technical and biological problems. Bioprosthetics had already been developed in the first period, in particular, it had been demonstrated that a human could survive with an artificial heart. Later, bioprostheses

* The author is grateful to S. Yu. Revskoy, a researcher in the laboratory of endocrinology, for the theoretical exploration of the probability of this phenomenon.

became widespread, as well as personal computers, which had a special block for recording all the information received by the given individual. These blocks were, in essence, a copy of the individual brain per se. In case of the development of random diseases of the brain, e.g., trauma, the device ensured the preservation of everything accumulated during previous life.

Burns and traumas, especially those associated with moving at high speeds, have remained and even increased, although they were already the main reason for death in young people during the first period. Naturally, the methods for treating injuries have improved. In particular, biosynthetic oncofactors are used on a wide scale to stimulate tumour-like (rapid) division of cells without transforming them into cancer cells, since these factors operate not inside, but outside the cell via special receptors on the cell membrane (Chapter 10).

Another direction in bioprosthetics is based on the principle of cloning individual cells for the reproduction of corresponding organs if necessary. After fertilization of the ovum and its first division, an individual identical organism develops if the distance between the cells increases for some reason. This is the origin of monozygotic twins. But potentially, each somatic cell stores genetic information, though blocked, which is necessary for the reproduction of a whole

organism. Already in the first period, relatively complex organisms of some species were reproduced from individual somatic cells. The only problem was to ensure reproduction of individual organs, which were necessary to replace the damaged organs, in an artificial medium, and to prevent the reproduction at once of all the organs because it was impossible to establish the border between the appearance of a twin that was identical to its "vegetative forefather" and the biotechnology of growing spare organs*.

It is impossible to describe here, even in general terms, everything that concerned the development of integral medicine. Therefore, we discussed briefly the development of studies relating to each model of medicine. Now let us discuss the major diseases.

These diseases gradually developed at a later and later age and then they stopped

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* As is known, this method can be applied, in principle, to produce a practically unlimited number of "vegetative" individuals similar to the initial one. This idea seems tempting to many: to "reproduce" at once 100 talented mathematicians (from a mathematician), or football players (from a football star). But life demonstrates that for progress in any field it is better to have 100 people with different talents than to have 100 identical geniuses. The latter case increases not only the number of outstanding discoveries but also the same errors and delusions.

to play an essential role in the life of humans, since the intensity of their development is conditioned, first of all, by the rate of aging, which was greatly retarded.

It should be stressed that without solving the problems discussed in this book, it is impossible even to dream of extending the limits of the human lifespan, though many scientists are prone to this kind of prognostication. The references these scientists make to the effect that there are no fundamental laws of Nature that would prohibit the creation of potentially immortal organisms, and that "atoms do not age", are groundless because even protein molecules age (e.g., because of thermal effects). Therefore, to expand the species limits of life, a combined approach must be applied, which takes into consideration the four basic mechanisms of aging and age-related diseases.

Obesity was the first disease to disappear. Since it had been the disease of diseases for centuries (if death due to external causes did not take one's life at a young age), the development of prediabetes and type II diabetes mellitus was retarded, as well as metabolic immunodepression, metabolic auto-immune disturbances, atherosclerosis, and cancrophilia. This was the reason for the sharp increase in the average and maximal lifespan of humans (see above). The climacteric also no longer presented a sig-

nificant problem because the reproductive period was long and, which is most important, it could be artificially prolonged. Climacteric neurosis was reliably prevented by medicines, as were mental depression, hyperadaptosis, and age-related hypertensive disease. The problem of cancer remained (and partially atherosclerosis), but did not present the problem it had been in the first period.

There is nothing strange in the fact that in the new period cancer remained a biological problem (as did atherosclerosis): random processes (i.e., random damage to the genetic apparatus, or the introduction of oncogene viruses into it) could not (like probabilistic events) be fully prevented or, all the more, eliminated. In other words, the possibility of the appearance of a cancer cell, or impairment of the arterial wall and proliferation of smooth muscle cells, which induces the formation of the atherosclerotic plaques, always existed. At the same time, substantial changes for the better appeared in all fields of oncology because development of the tumoral process was prevented in the majority of cases.

First of all, diagnostics was no longer based on such insufficiently sensitive methods as examination, thermography, computer tomography, accumulation of radioactive isotopes in the tumour, etc. These methods can detect a tumour when its

mass is sufficiently large (more than two million tumour cells). Instead, marker diagnostics was used, which is based on detecting special substances (usually oncofactors, see Chapter 10) that are released by the tumour. To detect these specific proteins, methods are used with a sensitivity of 10^{-15} g. Proceeding from the calculation for the determination of the marker of a trophoblastic tumour, i.e., chorionic gonadotropin (a hormone which is secreted by the tumour cell in a maximum possible quantity), it is easy to calculate that each cell secretes from 10^{-5} to 10^{-4} IU of this hormone daily. Thus, for a concentration of 1 unit of the hormone in one litre of blood, from 10 000 to 100 000 tumour cells (occupying a volume of only 0.05 mm^3) are required. And this is the testing limit for any marker.

Meanwhile, the natural immune system of a human can simultaneously neutralize about 10 000 tumour cells. At the same time, medicines ensured reliable protection in the rare cases when the immunological barrier of the organism was overcome and growth of the tumour focus occurred. But, if formerly preparations were used to fight the tumour cells, i.e., preparations that either killed these cells, or sharply inhibited their division (by facilitating favourable conditions for the activity of the natural protective forces, in particular, the activity of so-called specialized killer cells that

destroy tumour cells), now the treatment was determined depending on the mechanism of malignant transformation (see Chapter 10). When activation of the oncogene was caused by comparatively small changes in the chromosomal apparatus, e.g., by displacing the "resting" oncogene to another area where it fell under the influence of an activator (promoter), it was possible to return the transformed cells to their initial state by blocking the promoter. In other words, the purpose of treatment in many cases was not to destroy the cancer cell with medicines but to return its normal properties. In principle, such experiments had been carried out during the first period when it was demonstrated that the behaviour of tumours of embryonal origin could be normalized. It is interesting to note that vitamin A (and its derivatives, the so-called retinoids) played a major role in such treatment of the malignant cell.

Viral therapy also became widespread. As mentioned many times above, many oncogene viruses are able to insert themselves into the cell genome, which causes malignant transformation (Chapter 10). But this property of viruses could be applied to medicinal purposes only when it became possible to change the structure of the viruses as required. Viruses were created that were deprived of oncogenic properties but had the capacity to block the activity

of cell oncogenes, or natural tumorigenic viruses. Some "medicinal viruses" activated "immunity genes" that sharply enhanced antitumorigenic protection. In the majority of cases, it was possible to prevent cancer as a disease though it was impossible to eliminate the malignant transformation of cells.

Atherosclerosis was defeated, or, rather, it became possible to turn it into a very slowly progressing disease. The origin of atherosclerosis is conditioned by the mechanisms of all the four models of disease development, i.e., the ecological, genetic, ontogenetic, and involutionary (accumulational) models. It was most difficult to correct the latter mechanism because the element of impairment was inseparable from the nature of the biochemical processes (Chapter 11). Therefore, by the end of the second period, the situation became a little clearer with the involutionary (accumulational) diseases conditioned, in particular, by the accumulation of ballasts and cholesterol in undividing cells. When the debris filled almost the entire volume of the cells, it seemed that the natural dying away of the organism occurred.

But medicine was already on the threshold of new discoveries and new dreams.

As we approach the end of the book, let us return to current problems.

Medicine is entering a new stage that is

characterized by the extremely rapid accumulation of knowledge and developments in technology, primarily, biotechnology, as well as by serious organizational changes. The latter is most vividly illustrated by the increase in prophylactic screening of the population. But success is impossible without solving a series of problems. One of the most serious problems is the need to change the common preconceptions that people hold on the nature of the major human diseases.

The modern views were formed under the influence of victories over acute infections. In the past when there were no specific treatments, these diseases rapidly ended in either death or recovery. Later, it became possible to prevent the development of many infections by such means as vaccination. Modern means for the treatment of infections also render a relatively rapid effect.

Based on this experience, there is every reason to expect that medicine will develop short-term measures for the prophylaxis of the major noninfectious human diseases. But the prophylaxis of these diseases is similar to the prophylaxis of infections only within the limits of the ecological model of the origin of diseases, and even in this case, lasting efforts are required. In particular, such factors as an optimal diet, physical activity, and "control of oneself" should

become permanent components of a rational mode of life if one wishes to substantially decrease the threat of disease.

As stated in the Introduction, the achievements in medicine in the last century create the impression that it would be possible to gradually extend the average human life-span to 85 years or more by eliminating the ecological causes of the major diseases. Moreover, it is assumed that the period of life occupied by diseases will greatly decrease and that life will end with natural death: in other words, death from old age will occur without disease.

This author has already stated that despite the external logic and certain attractiveness of such a situation, it is unrealistic and incorrect. It does not take into consideration that ontogenetic and accumulational mechanisms form the entire complex of major diseases in each person irrespective of the ecological and genetic factors. If it were possible to study the structure of the survival rate graphs (see Fig. 1*a* and *b*) the following picture would form (Fig. 10). The principal causes of the major diseases, primarily, tumours, are genetic defects in childhood and youth; ecological causes of death dominate during the period of maturity, and then, if the ecological conditions are favourable, the main causes of death are determined by ontogenetic, and later, accumulational, diseases.

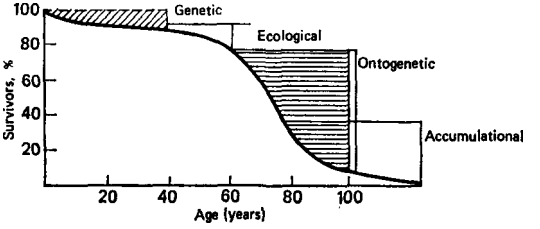

Fig. 10. Age ranges for various models of diseases on mortality.

Certainly, the rate of development of the diseases will retard with the elimination of unfavourable ecological factors. However, the "life thread" will still break, though not from old age. Death will occur because of the common course of chronic major diseases. Therefore, if the goal is to preserve satisfactory health up to the age of 85, the rate of aging, or (which is practically the same thing) the formation of ontogenetic and accumulational mechanisms of diseases must be retarded. These measures will extend the average lifespan as well as the maximal, i.e., the species specific lifespan. As stated above, the average lifespan is determined by ecological, and partially, genetic, factors, while its maximal value is determined by ontogenetic and accumulational mechanisms. Hence, the limit for a species lifespan is not a strictly fixed value. It can change depending on the

evolution of these mechanisms. As mentioned before, a substantial extension of the maximal human lifespan apparently occurred 200 000 years ago. It is believed that at that time, over the course of 100 000 years the maximal lifespan increased by 14 years. This increase is usually explained by improvement in the systems of protection against damage, which form the accumulational model of aging and diseases. This point of view explains the data that indicate that the greater the species lifespan, the higher the activity of the repair systems (Setlow and Hart, 1974) and antioxidant systems.

At the same time, it should always be taken into consideration that the maximal lifespan of primates, including humans, is negatively correlated with the rate of sexual maturation: the later the maturation of the organism, the longer the maximal lifespan. This dependence reflects the role of ontogenetic mechanisms in determining the species lifespan (Chapter 11).

Thus, this author has attempted to show that it is impossible to retard the appearance of the major noninfectious diseases, and, therefore, it is impossible to reach old age without suffering from any diseases, and moreover, it is impossible to increase the maximal lifespan if these four models of diseases are ignored when elaborating prophylactic and medical measures.

Currently, it is the ecological and genetic models of diseases that determine the strategy and tactics of modern medicine. For this reason the popularization of these problems is not required in a brief epilogue. Studies on the accumulational model are being carried out quite intensively. For example, it has been shown in animals that antioxidants retard the development of diseases that are associated with aging and increase the average lifespan (Harman, 1981), although the maximal lifespan does not increase. Naturally, the latter circumstance troubles the adherents of the accumulational model of aging. However, in this case the influence of the ontogenetic mechanisms of aging, which restrict the effectiveness of the antioxidant preparations, is not taken into consideration.

Hopefully, the concepts that substantiate the existence of the ontogenetic model will become attractive when the theoretical and practical consequences of this model, which are summed up in Chapter 17, are taken into consideration. It should be repeated once again that the ontogenetic model makes it possible to reject ideas on programmed aging and natural death, although aging and the major diseases emerge with a regularity characteristic of a genetic program because they are the by-product of the organism's developmental program. It follows from the aforementioned

that the maximal lifespan is not a constant value, which means that the limits of the maximal lifespan can be expanded on account of the influence of the ontogenetic mechanisms. It must be taken into consideration that living nature has no need to greatly prolong the period of life determined by the requirements of reproduction. This is a purely human problem because Homo sapiens, as a social species, has established additional goals beyond the requirements of self-reproduction. New methods must be elaborated to achieve the new goals. Certain results have already been obtained, such as retarded aging of animals through the administration of preparations that improve the metabolism of carbohydrates and fats, or reduce the secretion of insulin (Chapter 16)*.

However, this author foresees numerous and various difficulties in regard to utilizing the ontogenetic model associated with the necessity of studying its mechanisms and searching for new medicinal means (or utilizing the available means with new applications). Yet greater difficulties are purely psychological, conditioned by the

* Data on the use of medical preparations in clinical practice have been omitted. These aspects, as well as more strict substantiation of the problems discussed in this book, are presented in this author's monograph *Four Models of Medicine*, Meditsina, Leningrad, 1987 (in Russian).

necessity of rejecting many stereotypes. A few examples are given below.

It must be recognized that the criteria determining physiological norm in an adult should be the same for people of any age. This means that the age-related dynamics of these indices do not characterize the norm of aging but rather the degree of deviation from the norm, i.e., the rate of formation of the major diseases.

It should be understood that the age-related drift in the physiological indices is an indication for therapeutic correction, and when ecological means are ineffective (proper diet, increase in physical activity, rejecting harmful habits such as smoking, etc., in general, a change in the life-style) medical treatment must be administered. Moreover, prophylactic treatment in many cases (if not in all, though this is an individual matter dependent on age) is always required. The belief that medicinal interference is dangerous must be rejected because nature carries out its experiment under conditions of decreasing mortality due to external (ecological) causes, and the results are known: an increase in the lifespan is accompanied by an increase in the incidence of the major diseases.

The solution to these problems is greatly dependent on psychological factors, i.e., on the information available to the society, primarily, to its potential patients, and

on scientific substantiation of prophylactic treatment. The necessity of introducing the notion of "cholesterol diabetes" is an example of psychological reorientation, because both the doctors and the population will better then understand the necessity of decreasing the blood cholesterol concentration, analogous to the attempts now made to decrease the content of sugar in the blood of patients suffering from diabetes mellitus. This is all the more important, since "cholesterol diabetes", i.e., the age-related increase in the blood cholesterol content, develops in practically everyone. Conversely, the absence of this phenomenon characterizes a deviation that demands special assessment (Chapter 17). Hence, the purpose of this book is to familiarize people with a new approach to the development of the organism, in particular, accelerated development, the origin of major diseases, aging, and natural death. At the same time, the book introduces a new theory for the consideration of specialists. Certain difficulties exist in this respect because the specialization in medicine today hinders the perception of integral ideas.

Concerning the practical realization of these ideas, the following relatively simple problems must be solved at the initial stage: first of all, the minimal number of physiological parameters that are sufficient to describe the state of the energy and adapta-

tional systems of the organism must be determined (Chapter 13); second, the methods of examination must be standardized and their accurate reproduction over longitudinal observations ensured; third, the practically permissible degree of deviation from the ideal (or optimal) norm must be determined which establishes when it is advisable to start prophylactic treatment; and finally, a national program for the endorsement of available methods and the development of new ones for normalizing homeostasis must be established.

The popularization of scientific knowledge with the aim of rejecting some of the illusions inherent to various projects on the prolongation of life must also be undertaken. One of these illusions is the belief that there are adaptational and regulatory mechanisms that are mobilized during aging to preserve vital activity. This concept again endows aging with adaptive features, which do not exist in reality. Certainly it is psychologically convenient to think that something is continuously fighting against aging in the organism. In reality, however, certain compensatory mechanisms switch on during aging not because they are mobilized to fight against aging, but as a result of the physiological design of the organism, according to which each age-related deviation of homeostasis causes a reciprocal compensatory reaction, which itself is a

deviation of homeostasis, and so on. In the final end, this creates diseases of compensation (if assessed by the mechanism of their formation), or, in other words, creates an ontogenetic mechanism that terminates the existence of the organism. Without new scientific data and, moreover, without updating scientific theories on the reasons determining the average and maximal lifespan of humans, progress is obviously impossible. The data, opinions, hypotheses, and models presented in this book demonstrate that we all know enough to understand where our knowledge is missing and what is necessary to continue advancing along the path to integral and effective medicine.

Subject Index

SCIENCE FOR EVERYONE

Today, as a result of social progress and developments in medicine, the average human lifespan exceeds seventy years. Is this the limit? Why do we age? What mechanism lies at the base of this phenomenon, and are there means to retard it? What is the physiological norm for each age group?

The author, who is a professor and Doctor of Medicine, answers all these questions from the position of modern science.

The book is intended for doctors, biologists, and anyone who is interested in contemporary biomedicine.

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